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1967 Vol. 11 No. 1

JAPANESE JOURNAL OF OPHTHALMOLOGY

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Report 2. The Retino-Cortical Time

THE UNIVERSITY OF MICHIGAN
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Published by

J. J. O. Hongo Tokyo

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Acta Societatis Ophthalmologicae Japonicae .....Acta Soc. Ophth. Jap.

Japanese Review of Clinical Ophthalmology

(Ganka Rinsho Iho) .....Jap. Rev. Clin. Ophth.

Journal of Clinical Ophthalmology

(Rinsho Ganka) .....Jap. Clin. Ophth.

Folia Ophthalmologica Japonica (Ganka Kiyo).....Fol. Ophth. Jap.

Ophthalmology (Ganka) .....Ophthalmology (Tokyo)

Japanese Journal of Ophthalmology is issued four times a year, appearing in February, May, August and November. This Journal purports to represent unabridged English versions of most outstanding papers that have appeared in various ophthalmological journals in Japanese during the foregoing months of each issue. Papers are admitted by invitation of the Editorial Board. Titles and abbreviations of major Japanese ophthalmological journals are given above. The publication of this journal was supported partly by a grant in aid for Publishing Research Result from the Education Ministry.

Subscription price: six dollars per annum, including postage.

Publication Office

Japanese Journal of Ophthalmology

c/o Department of Ophthalmology, School of Medicine, University of Tokyo

Hongo, Tokyo, Japan

Correspondence relating to subscription should be sent to the sole agent, the **MARUZEN Co. LTD, P.O. Box 605 Tokyo Central, Tokyo.**

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PHOTOGRAPHIC REPRODUCTION OF FINDINGS ON A-BOMB CATARACTS AMONG HIROSHIMA A-BOMB SURVIVORS

Tsugio DODO

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The author and his staff have carried out observations on A-bomb cataracts at the Ophthalmology Clinic of Attached Hospital, Hiroshima University School of Medicine since the hospital moved to Hiroshima City in October 1957. As a result, it was found that the incidence sharply decreased among those exposed beyond a distance of 1600 meters from the hypocenter. The degree of A-bomb cataracts observed was classified into the 4 grades as shown in Table 1.

Table 1. Classification of A-bomb Cataracts by Severity

	Minute	Slight	Moderate	Severe
Opacity on inner surface of posterior polar capsule	+	+	+	+
Subcapsular opacity of posterior pole	−	+ (punctate)	+ (small clumps)	+ (large)
Shadows on transillumination	−	+	+	+
Photographic reproduction by transillumination	Impossible	Impossible	Possible	Possible
Subjective visual disorders	−	−	−	+

"Minute" means localized opacity on the inner surface of the posterior polar capsule which presents polychromatic sheen depending on the direction of observation which is visible only by slit lamp microscopy. "Slight" means that in addition to the findings of "Minute",there are small punctate opacities located in front of the posterior polar capsule, but hardly any shadows of opacities can be observed on transillumination. "Moderate" means that there are clumps of opacities located in front of the posterior polar capsule, and shadows of the opacities can be distinctly observed by transillumination. "Severe" means that so-called tuff-like opacities are located in front of the posterior polar capsule, and subjective visual disorders are present in this grade only.

The author had hoped to make photographic reproduction of these A-bomb cataract findings, and finally succeeded in capturing the images by transillumination with a fundus camera for the first time in May 1959. However, this means of reproduction alone was not sufficient, and further efforts were made toward photographing the slit image, but satisfactory

results could not be obtained. In April 1966, good results were obtained in making reproductions of representative cases with the use of a Zeiss photo slit lamp. One typical case each of moderate and severe grade cataracts will be introduced together with a brief explanation of the history and accompanied by photographic reproduction.

Case 1. A 22-year-old female (as of April 1966) with a modetate case of cataracts. She was exposed in the open at a distance of 900 meters from the hypocenter at the age of 1 year 11 months. Photos 1 and 2 were taken by the author and his staff for the first time by transillumination method on May 31, 1959, that is, at age 15, 14 years after exposure. Shadows of the small clumps of opacities in front of the posterior polar capsule were captured by transillumination photography from an oblique direction. (When this photography is applied from the front, the shadow of small opacities are obstructed from view by the catch light cast upon the cornea.) Visual acuity was 1.2 bilaterally.

The findings at the end of April 1966, 7 years later,were practically unchanged. The visual acuity of both eyes remained 1.2. Photos 3 and 4 show the small clumps of opacities immediately in front of the posterior polar capsule captured by oblique illumination. Photo 5 and 6 are slit images taken at the same time. Photo 5 is an optical section of the crystalline lens taken at 45° on the nasal side and vividly shows the localization of small clumps of opacities. Photo 6 is an optical section of the lens taken at 65° on the temporal side.

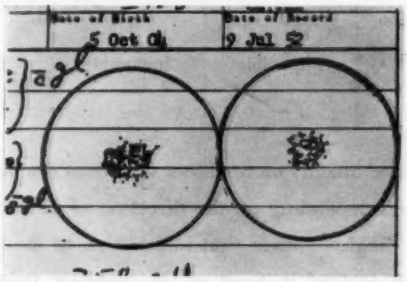

Fig. 1: Sketch of lenticular opacities of case 2, G.U. 46 year-old male (age as of June 9, 1952) by Dr. R.M. Sinsky.

Case 2. A 60 year-old male (as of April 1966), one of 3 severe cases observed by the author. As 5 of 6 eyes of these cases have undergone extraction of the cataractous lenses, the right eye of this patient is presently the sole remaining sévere case being followed by the author.

This patient was exposed at age 40 under the eaves facing the road at a distance of 820 meters from the hypocenter. He did not suffer thermal burns nor trauma, but suffered considerably severe radiation disturbances experiencing almost total epilation.

He was seen by Dr. D.G. Cogan at ABCC, Hiroshima in November 1949 and was recorded

Fig. 1 R eye

Fig. 2 L eye

Fig. 3 R eye

Fig. 4 L eye

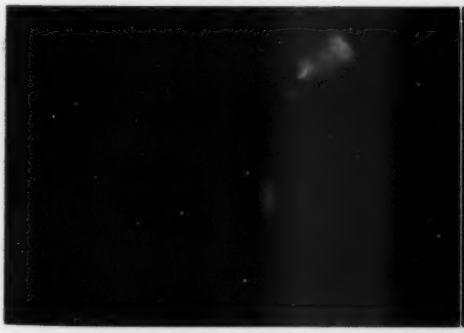

Fig. 5 R eye

Fig. 6 L eye

Fig. 7 R eye

Fig. 8 L eye

Fig. 9 R eye

Fig. 10 R eye

Fig. 11 R eye

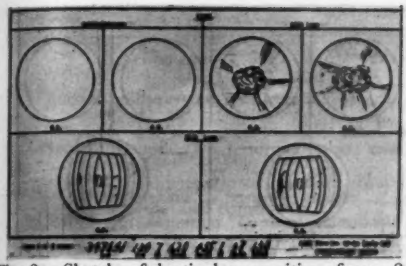

Fig. 2: Sketch of lenticular opacities of case 2, G.U. 50 year old male (age as of June 1, 1956) by Dr. D.V. L. Brown.

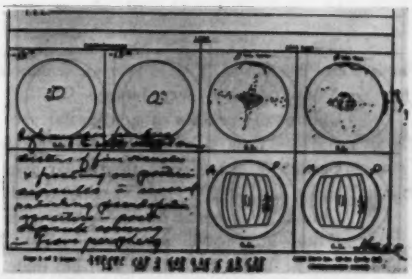

Fig. 3: Sketch of lenticular opacities of case 2, G.U. 51 year old male (age as of August 1, 1957) by Dr. C.W. Hall.

to have "early radiation cataract, slight". Subsequently in 1952, he was seen at the same place by Dr. R.M. Sinsky who drew a sketch of his observations which is introduced as Fig. 1 and made the notation "radiation cataract, moderate", but the patient's visual acuity at the time was given as 20/20 bilaterally. In 1956, Dr. D.V.L. Brown indicated visual acuity to be 15/20 on the right and 10/20 on the left, and drew the sketch shown in Fig. 2. About 1 year later in 1957, Dr. C.W. Hall drew a sketch of his findings which is presented in Fig. 3.

A review of these records makes one keenly aware of the difficulty and the introduction of error involved in reproducing findings.

Photos 7 and 8 are transillumination photographs taken by the author at the time of initial examination in August 1959. Corrected visual acuity was 0.7 on the right and 0.2 on the left. In September 1959, the left cataractous lens was extracted. Two years later (1961) corrected visual acuity of the right eye decreased to 0.4, while the left eye was 1.0.

At the end of April 1966 (5 years later), opacity of the right lens increased slightly as shown in Photo 9, but the corrected visual acuity remained 0.4. Photo 10 is a reproduction by wide slit image. Photo 11 is an optical section taken at 40° on the nasal side and shows a meniscus opacity in front of the posterior polar capsule.

Legends to colored Illustrations

Photo 1 and 2: Case 1, Y.S. 15 year-old female (age as of May 31, 1959)
A-bomb cataract—moderate
Clumps of opacities in subcapsular area of posterior polar region captured by transillumination.

Photo 3 and 4: Case 1, Y.S. 22 year-old female (age as of April 30, 1966)
Clumps of opacities in subcapsular area of posterior polar region captured by oblique illumination.

Photo 5 and 6: Case 1, Y.S. 22 year-old female (age as of April 30, 1966)
Clumps of opacities in subcapsular area of posterior polar region captured as slit images.
(Photo 5: Section taken at 45° nasal, 2X, Photo 6: Section taken at 65° temporal, 1X)

Photo 7 and 8: Case 2, G.U. 55 year-old male (age as of August 31, 1959)
A-bomb cataract—severe
So-called tuff-like opacities in subcapsular area of posterior polar region captured by transillumination.

Photo 9: Case 2, G.U. 60 year old male (age as of April 28, 1966)
So-called tuff-like opacities in subcapsular area of posterior polar region are slightly larger and more dense than those in Photo 7.

Photo 10 and 11: Case 2, G.U. 60 year old male (age as of April 28, 1966)
So-called tuff-like opacities in subcapsular area of posterior polar region captured as slit images.
(Photo 10: With broad slit; Photo 11: Section taken at 40° nasal, 2X)

FURTHER CLINICAL STUDIES ON THE ATOMIC BOMB CATARACT IN HIROSHIMA

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I. Preface.

At the 59th Annual Meeting of Japan Association of Ophthalmology in Kyoto, 1955, a lecture was given about the atomic bomb cataract in Hiroshima by the auther. The report was on the result of the examination of 520 atomic bomb survivors who consulted the Hiroshima Red Cross Hospital from June, 1953 to February, 1955. Additional 581 survivors were examined in the same way and at the same place during the ensuing one year and nine months. This report describes the total 1101 atomic bomb survivors during four years and nine months, from June, 1953 to March, 1958, compared with the previous report, and are referred to the other literature.

This report has been so made because it seemed to be necessary to conclude the history of twenty years after the atomic bomb explosion.

II. Result (Table I)

1. The incidence of the atomic bomb cataract.

Among the examined 1101 atomic bomb sufferers, 96 (8.7%) were diagnosed with certainty as atomic bomb cataract, and 121 (11.0%), as suspected. Compared with the previous

Table 1.

1. The rate of the atomic bomb cataract
   Total examined survivors.....1101
   Period.....June 1953—March 1958
   Place .....Hiroshima Red Cross Hospital
   Atomic bomb cataract.....96 (8.7%)
   Suspected atomic bomb cataract.....121 (11.0%)
2. Age and cataract
   Under 25 years of age.....45 cataracts (10.2%) in 443 survivors
   Over 26 years of age.....51 cataracts (8.8%) in 578 survivors
3. The exposure distance from hypocenter
   Within 2 Km .....79 cataracts (10.9%) in 723 survivors
   2 Km—3 Km .....11 cataracts (4.0%) in 278 survivors
   3 Km—4 Km ..... 3 cataracts (5.0%) in 60 survivors
   Over 4 Km ..... 3 cataracts (7.5%) in 40 survivors
4. Patient's location at the explosion
   35 cataracts (8.8%) in 400 outdoors
   61 cataracts (8.8%) in 701 indoors
5. Wound and cataract
   26 cataracts (8.8%) in 294 burned survivors
   53 cataracts (10.5%) in 507 traumatic survivors
   26 cataracts (7.0%) in 371 no wound survivors
6. Cataract and radiation symptoms
   600 patients (54.5%) with radiation symptoms in 1101 survivors
   68 cataracts (11.3%) in 600 patients with radiation symptoms
   28 cataracts (5.6%) in 501 patients with no radiation symptoms
   55 cataracts (19.6%) in 280 patients with epilation
   49 cataracts (16.3%) in 301 patients with fever
   43 cataracts (16.0%) in 269 patients with hemorrhage
   48 cataracts (13.8%) in 347 patients with diarrhea
   13 cataracts (10.8%) in 120 patients with abnormal menstruation
7. The visual acuity of the eyes with cataract
   32 (33.3%) patients with visual acuity of 1.0
   47 (48.9%) patients with visual acuity 0.9—0.4
   13 (13.5%) patients with visual acuity 0.3—0.1
   4 (4.1%) patients with visual acuity under 0.1
8. 231 Controls as non-exposed person
   16 cataracts with the same findings as atomic bomb cataract in 21 patients of pigmentary degeneration of retina.
   6 cataracts with the same findings as atomic bomb cataract in 19 patients of excessive myopia
   none cataract in 191 patients of slight refraction of conjunctivitis.

report, the percentage of atomic bomb cataract decreased remarkably from 26.8% to 8.7%, whereas, those with suspected atomic bomb cataract somewhat increased from 8.4% to 11.0%.

From the point of age, as shown in table 1, the percentage of young patients under 25 years of age was much greater than that of those over 2–6 by the previous survey and this time the relationship was reversed.

From the point of the exposure distance, among 723 sufferers within 2 Km from the hypo-

center, 79 (10.9%) were diagnosed as atomic bomb cataract, among 278 sufferers who were within 2 Km to 3 Km, 11 (4.0%), among 60 within 3 Km to 4 Km, 3 (5.0%), and among 40 over 4 Km, 3 (7.5) were so diagnosed. Compared with the previous report, the percentage is different, but it is the same that the percentage of the cataract patients within 2 Km is about two times as many as that of the patients from 2 Km to 3 Km.

In regard to the patient's location at the explosion, there is no difference between outside and inside. It is the same as the previous report.

As to the relation between the cataract and the radiation symptoms, among 1101 sufferers, 600 (54.5%) showed the so-called radiation symptoms. Among 600 patients, the atomic bomb cataract was found, in 68 (11.3%) cases. The rate is remarkably reduced compared with the previous report (33.2%). Among 501 sufferers without the signs or symptoms only 28 (5.6%) cases were diagnosed as having the cataract, and the rate is reduced also compared with the previous report (19.5%). However, it is true that the rate of the cataract patients with the symptoms is greater than that of without the symptoms. As to the symptoms, the cataract was found, in 19.6% of those with epilation, in 16.3% of fever, in 16.0% of hemorrhage, 13.8% of diarrhea, and 10.8% of abnormal menstruation. This is the same tendency of the previous report.

2. Atomic bomb cataract and visual acuity.

32 (about 33%) patients had visual acuity of over 1.0, 47 patients (49%) from 0.9 to 0.4, 13 (14%), from 0.3 to 0.1, and only 4 patients had visual acuity of below 0.1. In the previous report, there were 51% patients having visual acuity of over 1.0.

3. Findings of the atomic bomb cataract.

The detail slit-lamp examination, classification, and histological findings of the atomic bomb cataract was described in the previous report, but the classification by the slit-lamp examination, this time, is very much different from that of the previous report, in which, disciform type opacity was the most frequent (about 43%), followed by daughnut type (24%), and atypical form. This time, shown in fig. 1, granular atypical form (so called, calculus like opacities) are the most frequent (53 eyes, about 55%), followed by disciform (about 27%), vacuolmasstype, plate type, starfigure type, and anterior pole cataract.

Granular atypical form opacities (calculus like) .....53 eyes (A)
Disciform .....27 eyes (B)
Vacuolmass .....10 eyes (C)
Plate like opacities.....3 eyes (D)
Star figure opacities .....2 eyes (E)
Anterior pole cataract ..... 1 eye

4. Controls.

As controls, 231 nonexposed persons were examined by the slitlamp and, in 22 eyes

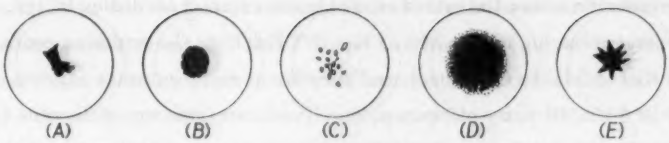

Fig. 1. Findings by Slit-lamp examination.

(9.5%), the same findings as atomic bomb cataract were observed, which is remarkable as mentioned in the previous report. Especially the findings of posterior portion of lens in the pigmentary retinal degeneration, which strictly resemble that of atomic bomb cataract and in addition to that, posterior pole cataract was found in 16 eyes of 21 patients (76%).

In 5 eyes of 19 excessive myopia, the same findings were observed. In 191 patients who had slight abnormal refraction or conjunctivitis, no abnormalities were found in the lenses.

III. Discussion.

1. The rate of atomic bomb cataract.

As mentioned in the previous report, it is natural that the rate depends upon how to select the examined persons. The more the number of the persons who lived within 2 Km from the hypocenter is, the more the percentage of the rate of the atomic bomb cataract becomes. Although the same like objects were examined in the same way, the rate of this time (8.7%) was much decreased compared with the rate of that (26.6%), the reason for which is that the diagnosis is strictly done and that only the atomic bomb cataract without doubt is counted. All that have some doubts are included in the suspected atomic bomb cataract, the rate of which is a little increased.

In regard to this rate, Kimura reported 9.8% in Hiroshima, K. Hirose, 40.8% in Nagasaki, Sinskey, as mentioned before, 84% in the epilation group in Hiroshima, Maetani, 26 cases (31.2%) out of 80 in Otake city, Asayama, et al., 9 cases out of 36 (25%). T. Tokunaga reported that among 1600 sufferers, he found 57.37% cataract who lived within 1.8 Km, and 45.84% cataract within 2.4 Km. in Nagasaki. I. Hirose et al. divided 800 persons in Nagasaki into 4 groups; first group, 43% of the persons with acute radiation disturbances who had lived within 2 Km from the explosion center, second group, 35% of the persons without the disturbances having lived within 2 Km, third group, 24% of within 3 Km to 4 Km, fourth group, 19% of controls had the opacities in the posterior potion of the lens. T. Dodo diagnosed 58 eyes (23.4%) as atomic bomb cataract of 248 eyes, and 28 eyes (11.3%) as suspected atomic bomb cataract, In regard to age, as mentioned in the previous report, the rate of atomic bomb cataract in young ages is more than in older ages, the reason for which is supposed that the young lens tissue is more sensitive to the radiation than the old one, so the damage is more severe. Toda, who examined the persons having experienced atomic bomb in their infancy,

withheld the conclusion about the rate of atomic bomb cataract according to age. Inada et al. examined the persons having lived within 1 Km or 2 Km from the explosion center and the persons within 2.5 Km to 5 Km as a control, and they found many cataract patients under 50 years old, especially in 10 to 19 years old group, they found an apparent difference from the other age groups according to the distance from the explosion center, and they found that the percentage of atomic bomb cataract in 10 to 19 years group showed inverted J curve. In regard to the distance from the explosion center, as reported before, in the sufferers within 2 Km there are an interrelation between the distance and the occurrence of the cataract, as Inada et al. showed statistically. Dodo, found the cataract in about 70% of the sufferers having lived within 1 Km from the center, 30% within 2 Km. T. Tokunaga, found 57.37% within 1.8 Km, 45.84% within 2.4 Km. Sinskey reported that the rate of the cataract was interrelated with the distance and the epilation.

Speaking of dosis of the radiation, Cogan described that γ-ray of the atomic bomb within 1. 97 Km from the center was about 600r, and neutron was estimated to be 3 to 15 rep. But there are many other opinions about the dosis, and N. Shono reported 600r of γ-ray and 280r of neutron like Arakawa's report. Nakaizumi, estimated 325r of total dosis, Tsuzuki, 600r. Dosis mentioned above is the momentary radiation one. Speaking of residual dosis, Shono reported that the induced radiation dosis was 100r during 100 hours within 0.5 Km to 1.0 Km and 60r during 10 hours. I. Hirose et al. described, in 178 cases, the relation between the incidence of stomic bomb cataract and the dosis of γ-ray and neutron which were estimated at A.B.C.C. in Nagasaki. The result was as follows; the cataract was found in 11.9% of 178 cases between 0 and 49 rad, in 26.5% between 50 to 99 rad, in 48.1% between 100 to 199 rad, in 55.3% between 200 to 499 rad, and in 90% over 500 rad. S. Sugimoto estimated 3400r at 750 meter from hypocenter, 560r at 1150 m (outdoor), 12.5r at 1800 m (indoors) and 18.4r at 1950 m (outdoors). Sinskey reported that there was statistically interrelation between the dosis of atomic bomb radiation and the subcapsular disciform opacities of lens. T. Tokunaga stated that severity of the cataract depended upon dosis of the radiation.

In regard to the exposure condition, there are no differences between the patients' location outdoors and indoors, i.e. 8.8% for outdoors and 8.7% indoors. According to M. Tsuzuki's report of radiation wound, there were no differences, 46.3% outdoors and 53.6% indoors, which shows that Japanese houses, made of wood, connot shunt out the radiation. This is the same result as the previous report.

Speaking of the wounds, there are no differences among burn, trauma and no wound, which is the same result of the previous report.

In regard to relation between the symptoms of the atomic bomb disturbances and the cataract, the rate of the cataract this time much lower compared with that of the previous

sarvey, the reason for which is that the diagnosis was strictly made and only atomic bomb cataract without doubt was counted. But, it is the fact that the rate of the cataract with the symptoms is two times as many as that without the symptoms, which is natrual that there are much more atomic bomb cataracts found in the patients suffering from systemic atomic bomb disorders. It agrees with Sinskey's statistics that the catract is found most frequently in the epilation group. There is an interrelation between the epilation and the rate of the cataract. Inada et al. reported no difference between males and females in occurrence of the cataract after the examination of 1031 persons.

As a control, 231 persons who have never experienced the atomic bomb are examined by the slit-lamp and in 9.5% of them were found the exactly same findings as the atomic bomb cataract, which is a very remarkable thing. Especially, in patients of pigmentary degeneration of retina, subcapsular granular plaques in posterior portion of lens like atomic bomb cataract are found in 7.5%. After all, in the cases of pigmentary degeneration, it is impossible to differentiate whether the cataract is the usual complication or the atomic bomb one. In cases of myopia excessiva, the same findings are observed, so the atomic bomb cataract should be diagnosed without those diseases. Maetani, reported that posterior lens opacities were found beyond physiological conditions in 14.29% of 40 controls and that posterior capsular and subcapsular opacities were found in all cases (5 cases) of retinal detachment, vitreous body opacities and pigmentary degeneration. I. Hirose, observed the posterior opacities of lens in control group. Sinskey, found the polychromatic granular plaques of the posterior subcapsular region of lens in 16 cases (10%) of 164 controls.

2. Atomic bomb cataract and visual acuity.

As already stated, the vision of atomic bomb cataract patients on the last investigation was more favourable than expected and there is no need to correct this time. Asayama et al. also reported there were no visual disturbed cases. I. Dodo mentioned that only 6 cases out of 248 eyes had heavy visual disturbances caused by the lens opacities. Hirose and Tokunaga reported the atomic bomb sufferes had visual disturbance in less than 5% of the cataract. In any way, it is fortunate that the lens opacities are limted to the posterior small region, but it is natural that the vision is disturbed when the opacities spread widely, and when the ones exist in anterior region. Tiny opacities of the atomic bomb cataract may become a cause of senile cataract, so it is necessary to take care of them.

3. Findings of atomic bomb cataract.

1) Findings by slit-lamp examination.

Compared with the last report, the granular plaque opacities were found much more frequently, and this opacities are the findings of atomic bomb cataract without doubt. Most of disciform and daugnut opacities are counted as suspected atomic bomb cataract this time.

According to the published litarature after that time, the calculus like opacities (the granular plaque opacities) ard the conclusive findings of atomic bomb cataract.

K. Hirose and T. Tokunaga, reported that, among 1600 sufferers in Nagasaki, the atomic bomb cataract occurring within 1.8 Km showed the spotty opacities in the dividing zone of lens, posterior subcapsular opacities and posterior subcapsular calculus like opacities, which they proved experimentally. Inada et al. divided the cataract into four groups, and mentioned polychromatic posterior plaque opacities as the typical atomic bomb cataract: 1) limit opacities, 2) polychromatic posterior plaque opacities, 3) roughness of posterior polychromatic capsule, 4) thick cortical opacities of unknown etiology. S. Sugimoto mentioned that typical atomic bomb cataract was posterior subcapsular calculous like opacities and spotty opacities. Maetani reported disciform and semi-disiform as collections of fine spots. Dodo mentioned that the limited opacities of posterior capsule and subcapsule were the morphological characteristics. Ichihara et al. thought, however, that disciform opacities were the first characteristic. Asayama and Sugimoto mentioned that spotty opacities had a meaning, too.

2) Histological findings.

It was H. Ikui who reported first the histological findings of atomic bomb cataract and he mentioned that maniscus-like changes in the posterior portion were characteristic. After that T. Dodo reported that four total extracted cataract were the posterior subcapsular degenerated nests of granular breaking and break-down of lens-fibers. T. Tokunaga, examined one atomic bomb cataract, mentioned fibril-dilatation of the posterior-lens, ectropic cells in the posterior capsule and abnormal swelling fibers of the subcapsule were characteristic, like the experimental radiation cataract. T. Maruta acknowledged vacuoles in the rediated posterior portion microscopically after the experimental radiation cataract in rabbits. Tokunaga, examined experimental radiation-cataract with the electron-microscope, acknowledged the changes in the posterior capsule of lens. First, dissociation parallel to the capsule one-quarter inside the capsule and power-like materials and fragments of lamelle scattered. Second, in the dissocition, ectropium of lens-epitheloid cells was found, and which become to fibroblast-like cells, and at last degenerated. I. Hosokawa reported that he observed the findings of the complicated cataract, enteropium of cell in the posterior subacapsule, formation of a pseudo-epithelial cell layer and collapse of cortical portion after cataract was brought on by Sr^{90} radiation on rabbits, and that various types of division in equator cell-nucleus were observed on the specimen of epithelial cells. T. Okamoto observed, after Sr^{90} radiation on rabbits, swellung and vacuoles of mitochondria and dilatation of endoplasmic reticulum, G. Okada, after Co^{60} radiation on rabbits, observed the irregularities of nucleus, cell-invasion to the posterior cortex, degeneration on the anterior subcapsule and equator-epithelium and dilatation of equator lens fibers. T. Tokunaga reported that mitochondria in epithelial-cell-plasma

and dilatation like vacuole of vesiculi after 24 hours of fast neutron radiation, and dissociation and coagulation of epithelial nucleole after 48 hours were observed.

4. Diagnosis of the atomic bomb cataract.

With the features mentioned above and the following points in mind, atomic bomb cataract may be diagnosed, but as mentioned in controls, the diagnosis must be carefully done especially in pigmentary degeneration of retina.

1) Sufferers within 3 km from hypocenter in Hiroshima.

2) Atomic bomb symptoms, especially epilation, fever, hemorrhage, diarrhea, and abnormal menstruation.

3) Findings by slit-lamp examination, posterior subcapsular plaques, disciform, opacities or collections of vacuoles.

4) To exclude intra-ocular lesions, especially pigmentary degeneration of retina and excessive myopia.

5) To differentiate from congenital retro-lental nodule, ring opacities and gray freckles.

5. Onset and prognosis of atomic bomb cataract.

It is an important and interesting problem to determine when the atomic bomb cataract begins and whether it advances or not. No one has studies just after the explosion, so I do not know when the cataract begins apparently. Tsuzuki reported that it began between the beginning, of the fifth month and several years. Shoji observed suspectable atomic bomb cataract forty days after the explosion. Ikui found typical atomic bomb cataract two years and two months later, extracted it totally and examined histologically. Hirose and Fujino's case was that visual disturbance appeared ten months later and atomic bomb cataract was diagnosed two years and four months later. Clapp mentioned the human latent period of radiation cataract was nine months and a half and eight years. Tokunaga reported that the serious case began earlier than ten months but that the latent period of the moderate and the light case was ten months or earlir than that, which he proved experimentally.

Next is the problem of whether the cataract advances or not. Hirose mentioned the cataract appeared in the sufferers within 1000 m of the hypocenter was progressive but that the ones over that distance was not. After that, Hirose and Tokunaga's additional report said that the cataract seemed to be stationary and not to be progressive and that, in animal experiments, the opacities were apparently reduced, and so the prognosis was not too bad. Ham and Dnaldson reported after examining 70 sufferers that the opacities of lens were reduced in 2%, slightly reduced in 17%, showed no changes in 36%, a little progressed in 15%, progressed in 26% and much progressed in 4%, which was a report made six years later. Sugimoto reported that serious cases were progressive. Dodo reported four cases which progressed slowly to necessitate extraction of the cataract when the vision was much disturbed after ten years and observed

the courses of the 15 patients, among whom the opacities did not change in 12 cases, and there were no cases showing reduction of the opacities. Sinskey mentioned that the opacities showed no progress or a slight progress during four yeras.

About 28 cases of certain atomic bomb cataract, I made a follow up from one year and a half to nine years. Among them, eight cases showed no chages in visual acuity and opacities (unchanged group), eight cases (changed group) no changes in visual acuity but changes in opacities, five cases (inproved group), some improvements in visual acuity and opacities, and 7 cases (aggravated group) showed some aggravations both in visual acuity and opacities. Sugimoto reported that he could observe no atomic bomb cataract turning into senile cataract. And Inada observed no difference between the sufferers and the nonsufferers over 50 years of age.

6. Cause of radiation cataract.

As mentioned previously, there are two opposite theories about the etiology of radiation cataract. The first is the direct theory that the radiation disturbs lens-tissue directly,to make opacities, and the second is the indirect theory that the radiation disturbs irido-ciliary body first, then makes change in the aqueous humor of anterior chamber and disturbs the metabolism of the lens to produce opacities. Talking about the literature published after the former report, Leinfelder reported that the radiation disturbed the lens-epithelium and the disturbed-epithelium came to the equator and made abnormal fibers to give rise opacities, which were pushed to the posterior pole. The epithelium at the equator of lens was the most sensitive to the radiation. When the lens was radiated partially, cataract occurred in only the radiated part. The radiated part protected from total cataract by an unknown mechanism. One quarter of the lens was radiated, regardless of the radiation dosage, total cataract never occurred. If the radiation was repeated every three months or more, total cataract hardly occurred, but, if less than that interval, it could occur easily. X-ray of more dosis than LD_{50} produced cataract and neutron less than LD_{50} could produce cataract and the cataract caused by neutron was much less reversible than by X-ray. He found the same findings in cultured epithelial-cells as in vivo. He also mentioned that no cataract occurred in pigeons and mice, the reason for which was that no pathologic fibers were made. He supported the direct theory. Tokunaga also supported the direct theory, searching experimentally and electron-microscopically that X-ray and neutron radiation made changes in the strongly sensitive RNA system of nucleolus, especially in epithelial-cells and young fibers having a nucleus, which might affect on the posterior portion of lens.

7. Experiments on cataract by radiation.

At any way, atomic bomb cataract is, briefly speaking, a disease disturbed lens tissue caused by γ-ray. β-ray and neutron. There are many reports about the experimental

cataract caused by X-ray, radio isotopes and neutron. According to literature on this subject published after 1955 in Japan, Tokunaga succeeded in producing cataract in a baby rabbit radiated one time 1000-X-ray. K. Atsumi made the cataract by injecting isotope P^{32} into the vitreous body. Tokunaga reported the calculus-like opacities appearing in the posterior subcapsular portion of lens by the radiation of 100 to 250 r every four or five days (total dosis 3200r). I. Hosokawa reported the cataract did not occur in rabbits by the radiation of Sr^{90} dosis of 3240 rep, and that the dosis over 6480 rep. gave rise to cataract in all cases. He supported the indirect theory according to the finding that the cataract was a complicated one.

K. Otsuka mentioned about the clinical findings of radiated rabbits, which received four times of 500 radiation and 1000r or 1500r radiation and produced anterior pole opacities or posterior suture fiber opacities and that it was necessary at least 1500r to make opacities in the anterior or posterior cortex and to make changes in the whole equator-portion and that the first change was found in the equator portion. T. Tokunaga gave 2000r to white rabbits and examined the cataract electron-microscopically as mentioned before. T. Okamoto reported that the dosis of 3240 rep of Sr^{90} did not make the cataract in white rabbits but the dosis of over 6480 rep made posterior-capsule cataract in all cases. He found swelling of mitochondria, vacuoles and endoplasmic-reticulum in epithelial-cells of the lens and these changes were irreversible and progressive. T. Tokunaga mentioned that, at 24 houres after the radiation of 400 rad to the right eyes of baby rabbits and 500 rad fast neutron to the left, swelling of mitochondria in the lens-spithelial cell-plasm and vacuole were observed and it disappeared after four days, and that dissociation of nucleolus and coagulation on the lens epithelium and young fibers-nucleus were observed and they advanced four days later. K. Shirabe mentioned as follows: White mature rabbits were radiated with fast-neutron, and in the group receiving lens than $3.2 \times 10n^{10}/cm^2$, after 17 to 53 weeks, small pionts of opacities and vacuoles, posterior-cortex-suture opacities and subposterior vacuoles appeared, in the group receiving $4.8 \times 10n^{10}/cm^2$, after 9 to 17 weeks, subanterior portion vacuoles sere observed, and equator changes were observed in only two eyes after 38 and 54 weeks.

In the low-radiated group, the opacities increased a little after appearance and were stationary there after in the high-radiated group, then increased after appearance and coagulated. In regard to the latent period, it was short in the high-radiated group and long in the low-radiated group. Y. Abe reported that β-ray cataract was found in 48 eyes out of 50 which were treated with β-ray for pterigium, after three years and six months and nine years. About the same thing, Y. Endo et al. found cataract in 9 out of 29 eyes observed over two years, and 8 out of 19 eyes observed over three years.

8. Therapy and others.

Treatment of atomic bomb cataract is the same as that of comon cataract. As mention-

ed before, fortunately, there are few serious cases in atomic bomb cataract. In the light cases, it is of course necessary to be put in good condition in general, and, locally the use of Vitamin-C, catalin, phacolin or glutathione may be effective. But in severe cases, there is no way but to extract the lens. S. Sugimoto reported that the cataract operation just after the explosion or during the heavy systemic atomic bomb symptoms had no good course and prognosis, but that the operation in the later period had good results. K. Otsuka mentioned as follows. About the meaning of oxidized-glutatione in the case of experimental-radiation-cataract, according to the total dosis and the rate of total volume, glutatione in the lens decreased remarkably, and that in the aqueous humor of the chamber increased and that in the vitreous body apparently decreased. In case of systemic medication, cysteine was more effective than glutatione, and cysteamine, than AFT. In local medication, glutatione and cysteine were more effective, and SH-compounds were effective in preventing the X-ray cataract. T. Dodo made a detailed report about 3 cases, in which the operation of cataract-extraction was carried out because the opacities increased markedly. All cases which were after 14 years of exposed had the same good post-operated results as with senile-cataract. Hirose and Tokunaga reported that there were no complications to make the operation difficult and that they experienced three cases (5 eyes) which regained good post-operated visual acuity.

IV. Conclusion.

1. In about 1101 survivors in Hiroshima who were examined from June, 1953, to March, 1958 (4 years and 8 months), clinical examination was carried out and the following results were obtained.

2. 96 (8.7%) patients were diagnosed as having doubtless atomic bomb cataract, 121 (11.0%), as suspected atomic bomb cataract, and total patients were 217 (19.7%).

3. In regard to the age, 10.2% were under 25 years of age, and 8.8%, over 26.

4. In regard to the distance, 10.9% had been within 2 Km from the hypocenter, 5%, over 2 Km.

5. There were no differences between those who were outdoors and indoors at the time of explosion.

6. There were no differences in the rate of atomic bomb cataract between the burn and the wound.

7. There was apparent difference between the sufferers having the radiation symptoms and the ones having no symptoms. The patients with epilation showed the highest rate of atomic bomb cataract (19.6%), followed by the patients who had fever, hemorrhage, diarrhea and abnormal menstruation.

8. In regard to the findings by the slit-lamp examination, granular opacity plaques in the

posterior subcapsular portion were the most frequent (55%), followed by disciform opacities, vacuole masses, plates, starform (33%), and anterior pole opacities.

9. Among them the visual acuity of over 1.0 was fortunately. 4 patients only had vision lower than 0.1.

10. In regard to the advance of cataract, 8 out of 28 cases showed nothing in particular. In the 8 cases, the opacities changed. In 5 cases, the opacities decreased. In 7 cases, the opacities were advanced and aggravated.

11. To decide on the diagnosis of atomic bomb cataract, pigmentary degeneration of retina and excessive myopia etc. must be eliminated. The distance from hypocenter and symptoms of atomic bomb disturbance are considered as the reference when characteristic posterior subcapsular granule-clot opacities were observed by slit-lamp, the diagnosis of the atomic bomb cataract may be decided without error.

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FLUORESCENT ANTIBODY STUDIES OF EPIDEMIC KERATOCONJUNCTIVITIS

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The epidemic keratoconjunctivitis (EKC) is being diagnosed clinically from clinical signs and epidemiologic evidences. The verified or etiological diagnosis of this entity is difficult, however. Isolation of the causative agent and/or demonstration of the rise in antibody titer during the illness will give the etiological diagnosis, but these procedures require a considerable length of time. The fluorescent antibody technique permits demonstration of viral antigen in infected cells, and this has offered a new method of rapid diagnosis of viral diseases. The

purpose of this study is, therefore, to demonstrate the adenovirus antigen in the conjunctival and corneal scrapings of EKC by means of the direct method of fluorescent antibody technique.

Materials and Methods

Virus: Strains of adenovirus type 8 and type 3 originally isolated by Mitsui et al.[4] in Japan and stored at −20°C were used in this experiment.

Cell culture: HeLa cells grown on coverslips in Leighton tubes were inoculated with either adenovirus type 8 or type 3. An intervals the coverslips were taken out, washed with phosphate-buffered saline (PBS), air dried, fixed in acetone at room temperature for 15 minutes, and stored at −20°C until used. The normal HeLa cells and those inoculated with herpes simplex virus were treated with the same way and were used as controls.

Scraping materials: Scrapings were taken with spatula from the upper or lower tarsal conjunctiva and, in some cases, from the cornea of the patients. The preparations were fixed in acetonn at room temperature for 15 minutes and stored at −20°C until used.

Antisera: Sera were prepared from patients of EKC with typical subepithelial punctate keratitis, approximately one month after the onset of acute follicular conjunctivitis. Neutralizing antibody titers of the sera were 40 against adenovirus type 8 and less than 10 against type 3.

Conjugation of fluorescein and globulins: Fractionation of γ-globulin from the antisera was carried out by the use of ammonium sulfate which was afterwards removed by dialysis. Conjugation was performed at a ratio of 1 mg of fluorescein isothiocyanate to 100 mg of protein by stirring at 4°C for 6 hours under the condition of pH 9.6 adjusted by carbonate buffer. Free dye was removed by passing the conjugate through a sephadex (G-25) and then DEAE cellulose column. Fluorescein-labeled globulin was absorbed twice with human brain powder, sealed in ampoules, and stored at −20°C. Before use it was thawed and diluted 2 to 4 times with sodium-PBS.

Staining: Slides were covered with fluorescein-labeled globulin at 37°C in a moist, chamber for 45 minutes and were then washed with PBS. The slides were mounted with buffered glycerol. As a control for the specificity of a staining reaction, adenovirus grown in HeLa cells was stained with fluorescein-labeled globulin added by the same amount of antiserum (one-step inhibition test). Observation was carried out under fluorescent microscope (Tiyoda FM 200 type). After fluorescent microscopy, the cells were stained with hematoxylin and eosin.

Results

Cell culture: In some of the HeLa cells inoculated with adenovirus type 8, fluorescent

particles appeared in the nucleus 6 to 8 hours after inoculation. Fluorescence became pronounced as the time passed and, 24 hours after inoculation, most of the cell nuclei were occupied by fluorescent masses (Fig. 1). Thirty-six hours after inoculation, cells assumed a round shape, and diffuse fluorescence appeared in the cytoplasm also. The fluorescence described above was considered as specific because of decay of fluorescence in preparations subjected to the inhibition test. The cells infected with adenovirus type 3 also exhibited the similar fluorescence. Fluorescence in cells infected with herpes simplex virus was so faint that it could be easily differentiated from that produced by adenoviruses. Normal cells set for a control study did not show any fluorescence.

Fig. 1. Fluorescent antibody staining of HeLa cells 24 hours after inoculation with adenovirus type 8. Adenovirus antigen is seen in the nucleus.

Scrapings: Fluorescence in epithelial cells was observed in about 50 percent of conjunctival scrapings obtained from patients clinically diagnosed as EKC during the first 2 weeks of the disease. One day prior to the onset, 2 specimens showed a positive result. These specimens were taken from the eye of patients whose fellow eye had already developed a flourishing conjunctival inflammation. The number of fluorescent cells varied case by case: some specimens showed a few fluorescent cells in one slide, and others many in one microscopic field. Fluorescence was observed either in the nucleus only or both in the nucleus and cytoplasm. In the latter case, fluorescence in the cytoplasm was usually weaker than that in the nucleus (Figs. 2, 4). In the cells whose cytoplasm had lysed, a particulate structure of fluorescence was observed in the remained nucleus (Fig. 6). Such nuclei were frequently seen in the mass of discharge and appeared to be in the advanced stage of degeneration caused by the virus. Fluorescent nuclei occasionally showed such changes as vacuolization, rearrangement of the chromatin, and aggregation of basophilic substances, when stained with hematoxylin and eosin (Figs. 5, 7). Cytoplasmic inclusions have not been observed in preparations stained with hematoxylin and eosin.

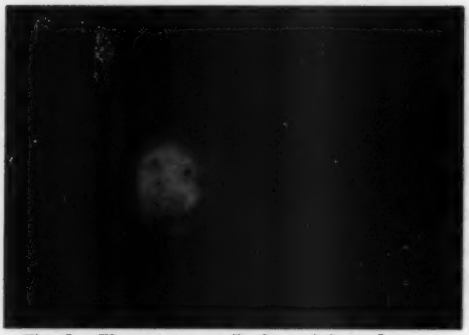

Fig. 2. Fluorescent antibody staining of a conjunctival scraping from EKC. An epithelial cells shows a strong fluorescence in the nucleus and a weak one in the cytoplasm.

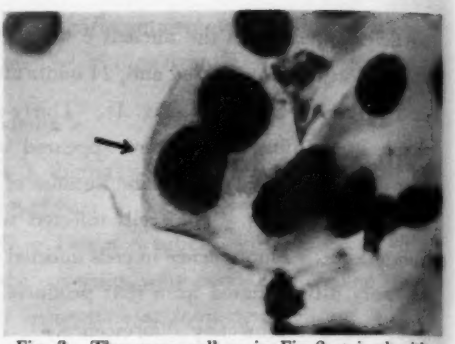

Fig. 3. The same cell as in Fig 2 stained with hematoxylin and eosin (arrow). There are normal cells which did not fluoresce.

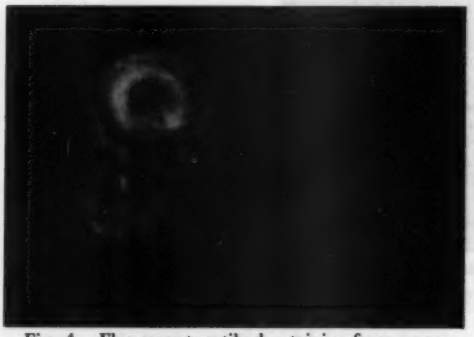

Fig. 4. Fluorescent antibody staining from a conjunctival scraping from EKC. Adenovirus antigen is seen in two cells.

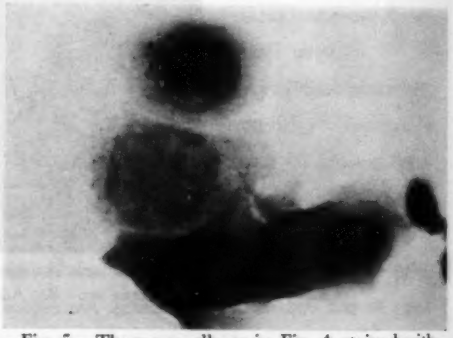

Fig. 5. The same cells as in Fig. 4. stained with hematoxylin and eosin. One nucleus contains a basophilic mass (upper). Another is enlarged and less basophilic (middle).

Fig. 6. Fluorescent antibody staining of a conjunctival scraping from EKC. Fluorescent particulate structure is seen in the nucleus.

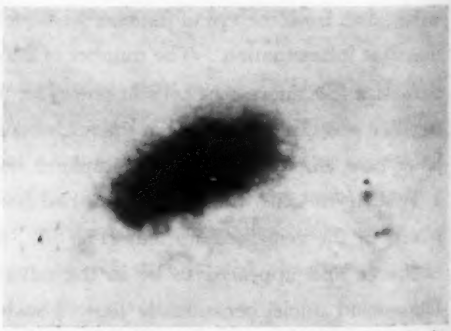

Fig. 7. The same nucleus as in Fig. 6. stained with hematoxylin and eosin. The cytoplasm undergoes lysis. The nucleus is filled with small vacuoles and granular masses.

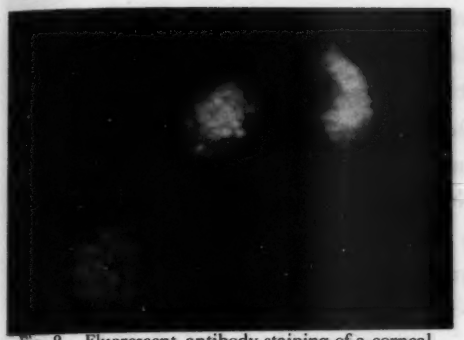

Fig. 8. Fluorescent antibody staining of a corneal scraping from EKC. Antigen is seen in three nuclei.

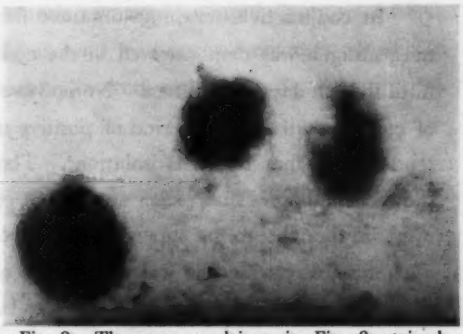

Fig. 9. The same nuclei as in Fig. 8. stained with hematoxylin and eosin. The cytoplasm is lysed. Vacuolization and a central basophilic mass are seen in one nucleus (middle), and other two are undergoing karyolysis.

Corneal scrapings obtained during the first 12 days of the disease also frequently contained fluorescent cells (Figs. 8,9). Even during the first few days of the disease when the cornea showed no abnormal findings by biomicroscope, a few fluorescent cells were observed in the scraping. Five to nine days after the onset of conjunctivitis, when the cornea showed epithelial erosion and infiltration, the corneal scrapings presented many positive cells. Two weeks or more after the onset of conjunctivitis, no positive cells were seen in the scrapings from the cornea, which showed typical subepithelial punctate opacities but no epithelial lesions on it. Morphology of fluorescent cells in corneal scrapings was the same as that in conjunctival scrapings. Scrapings from the conjunctiva and cornea of other conditions than clinical EKC and pharyngoconjunctival fever showed consistently a negative result.

Discussion

Antigen of adenovirus type 8 as shown by specific fluorescence was demonstrated in HeLa cells infected with homologous virus by means of fluorescent antibody technique using labeled antisera which were prepared from convalescent patients of typical EKC. Neutralizing antibody titers of the sera used were 40 against type 8 and less than 10 against type 3. Nevertheless, adenovirus type 3 showed a positive reaction to this fluorescent antibody. The similar fluorescent reaction of both types of adenovirus against the sera used, in spite of the definite difference in neutralizing antibody titer, seems to be attributed to the presence of group common antibodies of adenoviruses, such as CF antibodies.

In HeLa cells inoculated with adenovirus type 8 or type 3, viral antigen appeared at first in the nucleus as small bright dots and then developed into a mass occupying the nucleus. Diffuse fluorescence apeared later in the cytoplasm. These findings coincided with the established fact that the adenoviruses multiply in the nucleus[2].

In conjunctival scrapings obtained from clinical EKC during the first 2 weeks of the illness, antigen was demonstrated in the epithelial cells. Incidence of positive result was high until the 8th day of the illness. No positive result was obtained 2 weeks or more after the onset of conjunctivitis. This period of positive result by fluorescent antibody method show the same tendency as that by virus isolation[4]. There have been a few reports which employed the indirect method of fluorescent antibody technique for study of EKC[5,6]. Direct method, however, is thought to be superior to indirect one in its simple procedure for rapid diagnosis. Therefore, direct method was used in this experiment and it was proved to be useful for rapid diagnosis of EKC. However, it seems to be impossible to differentiate adenovirus type 3 from type 8 with the present method using human convalescent sera.

Specific fluorescence was also demonstrated in the corneal scrapings from the early stage of conjunctivitis prior to the onset of keratitis. The duration of positive reaction from the cornea was the same as that from conjunctiva. It was noteworthy that the viral antigen was demonstrated in the epithelial cells of the cornea without any manifestation of keratitis and that the antigen was negative in the corneal epithelium overlying typical subepithelial opacities developing at the later stage.

The intranuclear changes caused by adenovirus as seen by light microscopy have been reported in tissue culture studies[1]. Sugiura[5] pointed out that the same change could be seen in epithelial cells in conjunctival and corneal scrapings taken from EKC. In the present experiment, specimens examined by fluorescent antibody method were later stained with hematoxylin and eosin. At times, cell nuclei which gave fluorescence showed intranuclear changes such as vacuolization, rearrangement of the chromatin, aggregation of basophilic substance, and karyolysis. In specimens taken from patients with typical EKC, Imre et al[3]. observed the cytoplasmic fluorescent bodies which corresponded to inclusion bodies revealed with the subsequent Giemsa staining. In the present experiment, viral localization was noted in the cytoplasm, however, cytoplasmic inclusions have not been observed in preparations stained with hematoxylin and eosin.

Summary

Immunofluorescence for EKC was attempted by direct method using human convalescent sera which contained neutralizing antibody against adenovirus type 8. In HeLa cells inoculated with adenovirus type 8, specific fluorescence was observed to appear in the nucleus at first and later in the cytoplasm. The reaction was similar with adenovirus type 3, but not with herpes simplex virus.

This method was applied clinically for diagnosis of adenovirus infections. The adenovirus antigen was demonstrated in epithelial cells in the conjunctival and corneal scrapings taken

from clinical EKC. This method was, therefore, considered useful for rapid diagnosis of EKC.

Fluorescent cells in the scraping occasionally showed intranuclear changes specific to adenovirus when stained subsequently with hematoxylin and eosin.

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TAKAYASU'S DISEASE. A FLUORESCEIN ANGIOGRAPHIC STUDY

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The disease of Takayasu, of which the first description dates back to 1908[1], is now understood as ocular manifestation of a systemic process in which the major branches of the aorta as well as the aorta itself undergo a slow occlusive change through giant cell infiltration and later fibrosis of the wall with thrombosis formation. The eponym of pulseless disease is the most widely accepted denomination of the syndrome[2]. Through fluorescein fundus angiography of various stages of the disease the present author attempted to elucidate how the fundus reacts against the chronic and progressive reduction in the blood supply to the eye which ultimately results in the classical picture described by Takayasu. The present paper also shows that the pathological fundus process of this disease, at least in its early stage, is a reversible one and is amenable to cure through pertinent vascular-surgical interventions.

Methods

Fluorescein fundus photography was conducted with a Japanese fundus camera (Olympus Co., Model GRC) with necessary modifications developed by the present author[3~6]. No. 18 (blue) and No. 17 (green) Fuji gelatin filters, which have narrow spectrum range with their peaks at 470 and 520 mμ respectively, were built in. As the green filter in the camera was positioned where the light beam coming back from the fundus to the observing finder as well as to the film passed through the filter, the fluorescein pattern in the fundus was clearly monitored through the finder at the same time as serial photographing was conducted. As a rule 8 cc of 10% fluorescein aqueous solution, to which 2 cc of 0.5% Metoclopramide (Primperan[R]),

a centrally acting antiemetic, was added, was rapidly injected into the antecubital vein. Photography was conducted at a minimum interval of 7 seconds using 35 mm Kodak Tri X Pan film which was force developed.

Cases and Findings

Six cases with established Takayasu's disease were studied by means of fluorescein. All of them happened to be females. In all cases systematic aorto- and angiography had been conducted and the presence of either narrowing or constriction of the common carotid and the subclavian artery had been confirmed. The radial pulse was either absent or extremely weak in all of the cases. In two instances (Case 1 and 4) by-pass graft was implanted between the descending aorta and one of the internal carotids using Teflon artificial vessel to

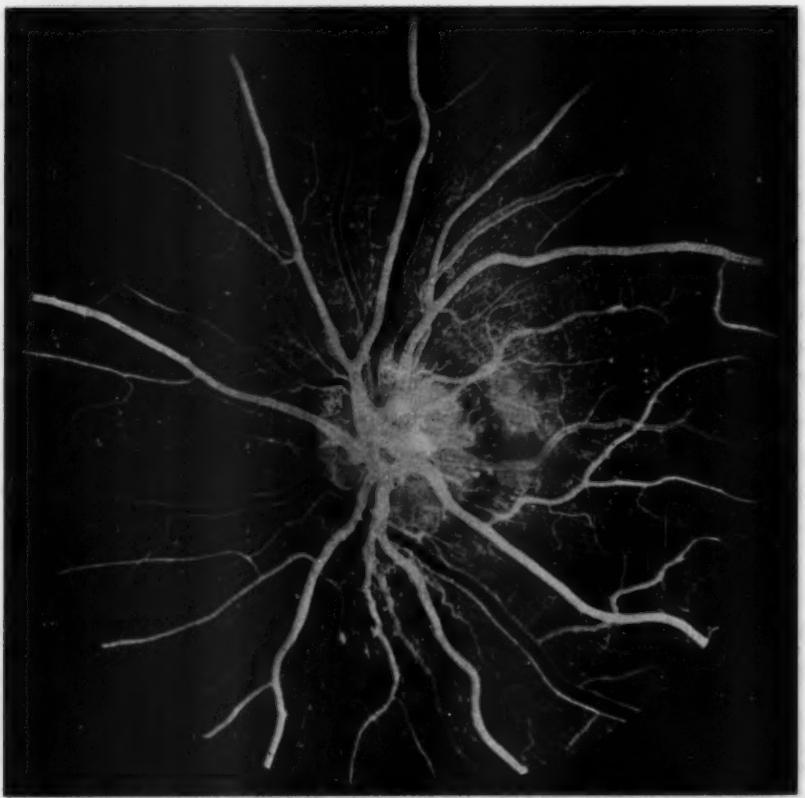

Fig. 1. Fluorescein fundus appearance in Case 1, OS (arterial phase). Numerous microaneurysms are identified in the retina as well as over the optic disc. The retinal veins, which appear laminated, show irregular dilatations.

establish collateral circulation from the aorta and the intracranial circulatory system with beneficial results as will be described.

Fig. 1. shows the fluorescein picture during the arterial phase of Case 1, an 18-year-old female (K.F., 66–00532). Asthenia of upper extremities and the jaw during chewing and intermittent attack of faintness were the sole subjective symptoms before seeking medical advice. Ophthalmological studies revealed normal visual acuity and visual field. There was moderate mydriasis. Intraocular tension was excessively low at 6 mmHg OD and 4 mmHg OS through applanation. Fundus finding was abnormal and was almost identical for both eyes (Fig. 2). Numerous haemorrhagic dots and soft exudates were scattered throughout the posterior fundus. There was slight hyperemia of the optic disc. While retinal arteries showed almost normal appearance, the veins were engorged and showed localised irregular sausage-like dilatations. Through biomicroscopy of the fundus slowing of venous blood flow and sludging formation within the veins were observed. Quantitative measurement of retinal arterial pressure was impossible as the arteries showed immediate collapse upon slightest pressure to the eyeball.

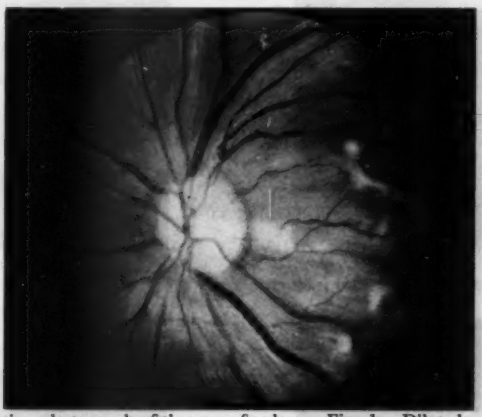

Fig. 2. Routine photograph of the same fundus as Fig. 1. Dilated retinal veins, dot haemorrhages and soft exudates comprise cardinal findings.

Fluorescein studies of the fundus, which was conducted 7 times during a period of 2 months, showed consistently pathological findings. While the arm-to-retina circulation time averaged 18 seconds, the laminar flow in the major retinal veins usually lasted 50 seconds, an indication for slowing down of blood flow in the retinal veins. The white patches or soft exudates in the retina did not fluoresce and were indicated through ill-defined turbidity masking the underlying retinal vascular pattern. Numerous fluorescent dots made their appearance over the whole posterior fundus. Some of them corresponded in location to the

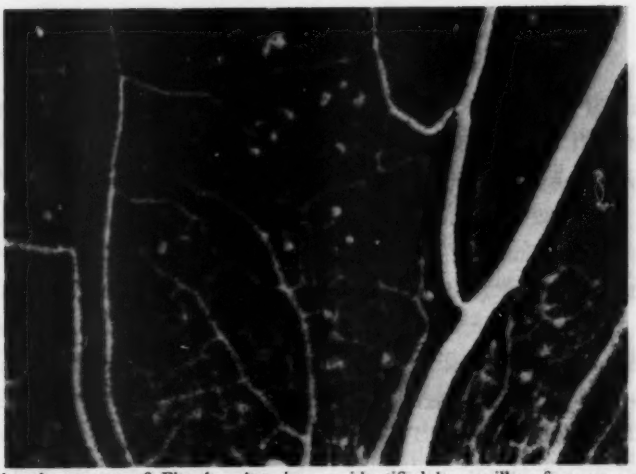

Fig. 3. Partial enlargement of Fig. 1. Arteries are identified by capillary-free zone on both sides. Fluorescent dots have direct connections with capillaries, a sign that they are real capillary microaneurysms.

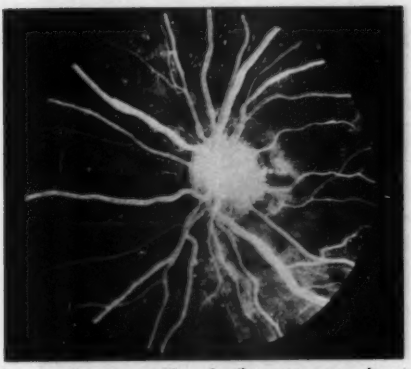

Fig. 4. Same as Fig. 1 (late venous phase). Leakage of fluorescein is taking place from veins and microaneurysms.

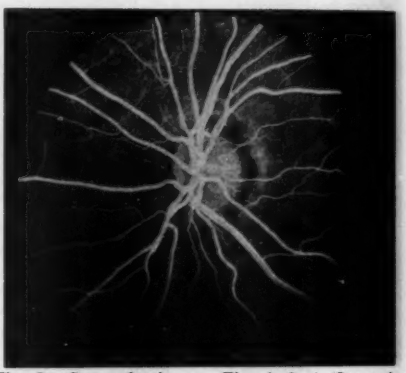

Fig. 5. Same fundus as Fig. 1 & 4 (3 months after surgery). The microaneuryms have completely disappeared following improved retinal circulation. Decrease in caliber of retinal arteries and veins has also occurred.

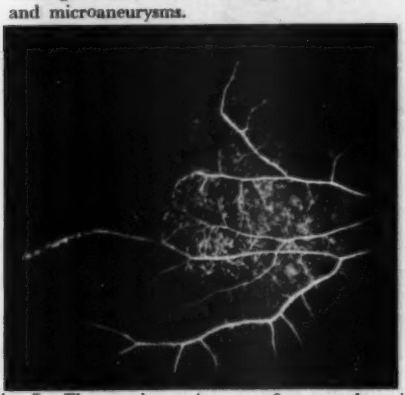

Fig. 6. Fluorescein angiogram of temporal periphery of Case 2. Arteries and veins are communicated through arched bridges formed by opening up of preexisting channels. Distal to the anastomosed vessels the retinal vessels are obliterated except main venous stems.

Fig. 7. Fluorescein angiogram of Case 3. Retinal venules show bead-like irregular widenings.

ophthalmoscopically observed haemorrhagic dots. The fluorescent dots during the early arterial phase were sharply defined, did not show appreciable change in size during the arterial and the venous phase, had a diameter ranging from 1/50 PD to 1/150 PD and a majority of them had direct connections with capillaries, as partially enlarged photograph (Fig. 3) of Fig. 1 will show. These characteristics of fluorescent dots indicate that they are true capillary microaneurysms. Towards the late venous phase leakage of fluorescein through the venous wall takes place where the local dilatation is prominent (Fig. 4).

Surgical correction of obstructed arteries was conducted after 2 months of futile systemic steroid therapy. A Teflon tube was implanted to bridge between the descending aorta and the bifurcation of the left common carotid artery. As there was also coarctation of the aorta where it passes through the diaphragm, similar by-pass graft was implanted to reach the abdominal aorta. The retinal arterial pressure was immediately normalised as a result of the operation. 9 days after surgery, the retinal arterial pressure measured 54/25 mmHg OD and 95/45 mmHg OS. 13 days after the operation, the soft exudates as well as haemorrhagic dots had completely disappeared. The retinal veins resumed normal caliber and the fundus was practically normal in appearance. Fluorescein studies conducted on the 16th postsurgical day showed complete disappearance of microaneurysms. The laminar flow in the retinal veins lasted only 12 seconds which indicate that the blood velocity in the veins had normalised. In Fig. 5 the fluorescein picture taken 3 month after the operation is shown. Comparison of the picture with earlier ones show striking diminution of venous caliber by about 20%, disappearance of capillary microaneurysm, lack of extravasation of fluorescein and a marked diminution in the visibility of individual capillaries.

Fig. 6 shows the peripheral fundus of Case 2, a 22-year-old female (K.N., 66–02075). While posterior fundus shows slight engorgement of veins as well as increased visibility of capillary networks, arched direct communications have formed between arterial and venous branches in the temporal periphery. Distal to the anastomotic communications there is a total closure of retinal vascular networks excepting a few venous trunks. Besides capillary microaneurysms, the veins show continuous spherical bulgings like rows of beads or strings of pearls. Similar findings have been also observed in Case 3, a female of 42 years of age (U.K., 65–04624) in whom the disease was detected 4 years before (Fig. 7). In Fig. 8 the arteries can be identified by the capillary-free zone around it. The picture shows that aneurysms have chiefly formed on the venous side.

Figg. 9 and 10 represent routine and fluorescein fundus of the right eye of Case 4, a 37-year-old female (S.A., 65–04083) in whom visual disturbance set in 5 months before as a result of retinal haemorrhage and Takayasu's disease was discovered. A bunch of tuftlike capillary loop is observed protruding from the optic disc into the vitreous. These vascular loops

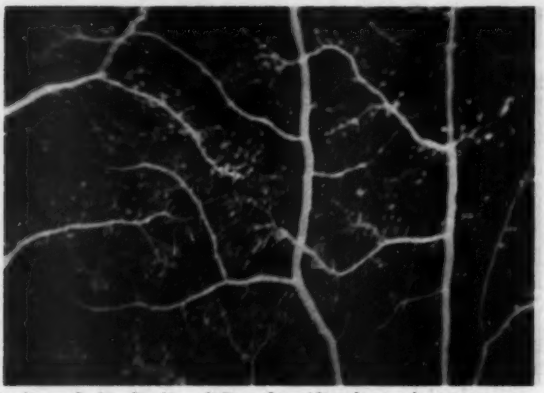

Fig. 8. Enlarged view of the fundus of Case 3. Abundant microaneurysms and dilatations of vessels are present in the peripheral fundus. Retinal artery is identified by capillary-free zone around it. Microaneurysms are mainly on the venous side.

show instant filling of fluorescein from the early arterial stage on. Numerous microaneurysms are found in the peripheral as well as posterior fundus. The left eye was bizarre in its appearance through fluorescein studies as effective retinal circulation took place only in the peripapillary area and at an extremely low speed. At the first fluorescein study the retinal vessels failed to fluoresce at all and at the second attempt two weeks later it took 3 minutes for the veins to fill with fluorescein after appearance of fluorescence in the arterial tree. Moreover, fluorescein filling occurred only in major retinal vessels alone, as other minor retinal vascular network remained obliterated. In the more severely affected left eye there was rubeosis of the iris associated with total goniosynechia reaching well over the line of Schwalbe. Cataract developed six months later which made fundus examination of the left eye impossible. By-pass graft operation was made 13 months after the first examination, which resulted in absolute glaucoma in the left eye 5 days after the operation and in normalisation of the fundus in the right eye (Fig. 11).

The fundus of right eye of Case 5, female of 26 years of age, is shown as Fig. 12. She sought medical advice on account of visual failure and was diagnosed as Takayasu's disease. At the time of first examination the visual acuity OD was already reduced to O. The retinal veins show engorgement without being tortuous. A round wreath-like capillary network has formed on the optic disc. The retina shows fine folds running radially from the disc. Ill-defined white patches as well as dot haemorrhages are scattered over the posterior fundus. On magnified inspection of the fundus sludging and fragmentation of red blood cells have formed within the veins. The left eye is almost identical to the right with the difference that a bunch of capillary loops protrudes from the optic disc into the vitreous. The arm-to-retina circulation time as studied by fluorescein measured 40 seconds OD and 15 seconds OS.

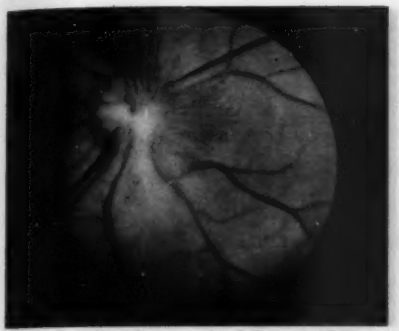

Fig. 9. Routine photograph of Case 4 (OD). A bunch of capillary loops have formed in front of the optic disc reaching anteriorly into the vitreous.

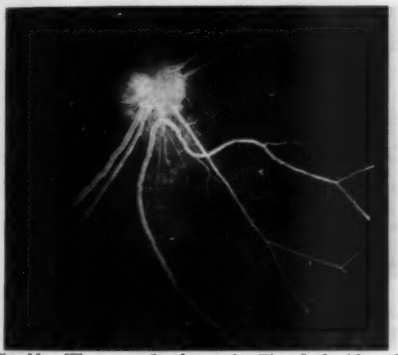

Fig. 11. The same fundus as in Fig. 9 & 10. (2 months after surgery). Retinal microaneurysms and prepapillary vascular loops have disappared.

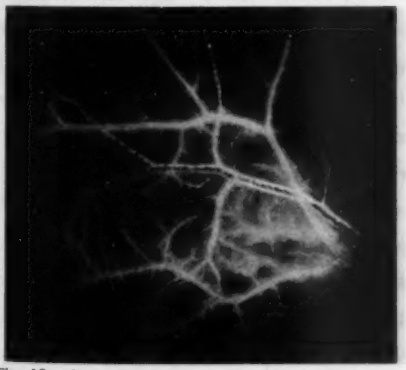

Fig. 13. Same fundus as in Fig. 12 & 14 (upper temporal periphery), late venous phase. Retinal arteries show retention and leakage of fluorescein from their wall. Veins show irregular filling-in due to sludged blood.

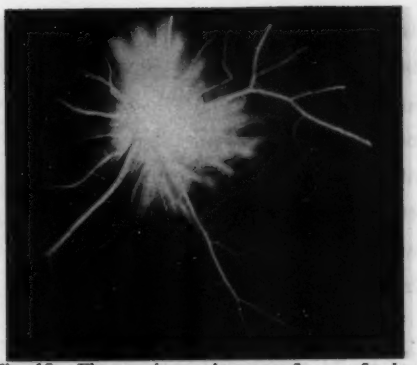

Fig. 10. Fluorescein angiogram of same fundus as Fig. 9 (Case 4). Arterial phase. The looped newly formed vessels have promptly filled with fluorescein. Numerous microaneurysms are identified.

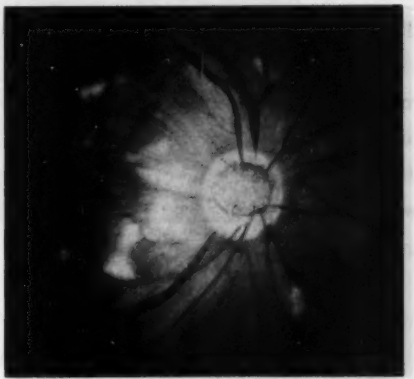

Fig. 12. Routine phogotraph of Case 5 (OD).

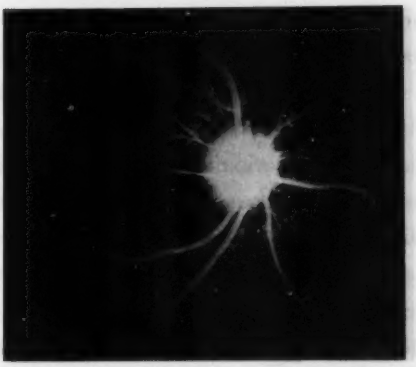

Fig. 14. Fluorescein angiogram of same fundus as Fig. 12. Arterial aneurysm is seen to the right (nasal) to the disc.

In the right eye the arterial phase lasted strikingly long: the fluorescein filling of retinal veins began 40 seconds after the first appearance of fluorescence in the optic disc. In the left eye the arterial phase lasted for 15 seconds. As particular fluorescein finding in this case the majority of observed aneurysms had direct connections with arteries. They were larger than usually observed capillary microaneuryms, the largest of them having a diameter of 1/15 PD, or about 100 microns. Towards the late venous phase fluorescein began to leak out of arterial wall, while it tended to accumulate within the venous wall presenting a superficial resemblance to laminar flow observed in normal eyes.

Fig. 14 shows a composite fluorescein fundus finding in Case 6, a female of 20 years of age (M.E., 63–03027). The diagnosis of pulseless disease had been made 18 months before when she visited an orthopaedic surgeon due to sudden numbness in the upper extremities. At the time the fluorescein study was made the visual acuity was already reduced to 0.02 in each eye. There was total goniosynechia formation in both eyes as well as ectropium and rubeosis of the iris.

Fluorescein studies (Fig. 15) show that the major retinal artery and vein have formed anastomosis at places where they intersect. No effective blood flow takes place distal to the anastomoses. Retinal vessels of lesser order do not fill with fluorescein, as circulation seems to be conducted only through the trunks. Because of rapid leakage of fluorescein through the vascular wall the vessels are represented as having only a vague, blurred contour. A few microaneurysms are present.

Discussion

The disease of Takayasu is a slowly progressive one for which various stages can be arbitrarily classified according to the fundus picture observed ophthalmoscopically. The currently accepted classification is the one proposed by Yanagida which sets three stages for the disease. To cite:

Stage 1. There is a slight hyperemia of the optic disc. The retinal veins are strikingly dark red in color, are engorged and may show bead- or spindle-like localised dilatations. Capillary neovascularisations may take place near the disc or in the peripheral fundus. Ill-defined grayish patches and haemorrhagic dots, some of which simulate microaneurysms, are seen dispersed in the posterior fundus. The central arterial pressure is excessively low and is quantitatively immeasurable, as the retinal arteries show immediate collapse upon slightest pressure to the eyeball. Though the visual acuity and the visual field is practically normal, sudden diminution in vision with faintness sets in through upward movement of the head.

Stage 2. The pupil is mydriatic and shows sluggish reaction to light. Atrophy of the iris sets in. The clouded patches of the retina as well as haemorrhagic spots become more conspi-

Fig. 15. Composite fluorescein angiogram of Case 6 (OS). Retinal vessels of lesser order have closed up so that circulation is conducted by main vascular stems only. Anastomoses have formed between artery and vein at their crossings. Fluorescein is leaking out of retinal vessels.

cuous as in Stage 1. Capillary loops may form around the disc through enlargement of pre-existing vessels. Anastomosis formation occurs between artery and vein in the periphery and around the disc. Vitreal opacity may be present. Sludging of blood may be seen opthalmoscopically in retinal vessels. The vision is considerably diminished.

Stage 3. There is extreme mydriasis with abolished light reflex. Rubeosis of the iris is the usual occurrence. The retinal arteries are indistinguishable from retinal veins. They form wreath-like anastomosis formations around the optic disc. The vessels peripheral to the anastomosed ones are extremely attenuated. Some look like mere white lines and the majority become invisible through ophthalmoscope. Through progression of the disease the condition is often complicated by retinal or vitreal haemorrhage, retinal detachment and complicated cataract.

Both eyes are usually involved. The intraocular tension is subnormal from the initial stage on. It may rise to the normal level or even glaucoma may set in it Stage 3 through extensive goniosynechia formation. In addition to the above ophthalmoscopical findings there-

are other systemical signs. Shimizu and Sano listed absence of radial pulse, peculiar eye signs and increased carotid sinus reflex as the triad for the pulseless syndrome. The patient often complains of fatigue of upper extremity, eye pain, vertigo, faintness, decrease of vision when looking above. Psychic symptoms as aphasia or amnesia may set in. Young females after puberty are predominantly affected. The prognosis as to vision and/or life is invariably poor. There is an atypical group of the disease in which the descending aorta and its tributary arterial branches, e.g. the renal artery, are chiefly affected by the same pathological process. In this case hypertension in the upper extremity and the head is the usual consequence and the fundus process is usually that of symptomatic hypertension. This atypical group lies out of scope of this paper and by common agreement we reserve the designation of Takayasu's disease for the above ocular condition in which impaired blood supply to the eye is the fundamental cause.

The Case 1 described in the present paper can be said to be a typical instance belonging to the first stage of Takayasu's disease. Through correlation of the fluorescein picture with ophthalmoscopical findings an attempt can now be made to elucidate the underlying pathological process of the fundus. The comparison of routine and fluorescein fundus photograph shows that each "haemorrhagic dot"in the former has consistently its counterpart in the latter in the form of capillary microaneurysms. As the microaneurysms are about three times numerous as the "haemorrhagic dots" and as the latter is considerably larger in size than the former it can be concluded that the red dots observed in stage 1 of Takayasu's disease represent haemorrhages which seeped out of some of microaneurysms. Measurement of microaneurysms in enlarged photographs has shown the microaneurysms to be 1/50 to 1/150 PD, or 30 to 10 microns, in diameter, while the haemorrhagic dots have a diameter of 1/40 to 1/15 PD, or 40 to 100 microns.

The grayish patches which were peculiar features for stage 1 of Takayasu's disease were either not represented by fluorescein pictures or only sightly indicated by blurring of underlying retinal capillary configuration. This finding shows that the clouded patches are not real "exudative" foci, as has been postulated by some authors, but mere opacities in the nerve fiber layer corresponding to localised tissue swelling due to ischaemia.

We have seen as a matter of particular importance that the ophthalmological findings in case 1 and 4 became normal within a week after adequate fundus circulation was reestablished through vascular-surgical interventions. Fluorescein studies show, as comparison of Fig. 1 (before operation) and Fig. 4 (1 week after operation) indicates, the complete disappearance of microaneurysms. At the same time, the irregularly engorged veins became narrower by 20% to assume normal caliber. These observed improvements in the fluorescein picture have been brought about by sheer increase in retinal arterial tension and associated blood supply to the fundus. We can state, inversely, that chronic ischaemia had chiefly been responsible for

the causation of capillary microaneurysms and the observed irregular dilatations of veins. The mode of onset of ischaemia to the retina seems to play an important role in the causation of microaneurysms. In Takayasu's disease the gradual decrease in retinal arterial pressure is a very chronic process. This will explain why one does not find microaneurysm formations in more acute occlusive disorders of the fundus as embolism of the central retinal artery.

In Fig. 7 & 8, which belong to more advanced stage of the disease than Fig. 1, we find that the capillary is not the sole vessel that reacts with aneurysm formation against chronic ischaemia in the retina. It is seen that retinal veins, and those in the peripheral fundus in particular, are capable of aneurysm formation and of assuming bead-like appearance. In more advanced cases, as in case 5, retinal arteries show saccular pouching of its wall. When one correlates these observed facts with the severity and duration of the disease, there seems to exist a regular order for various retinal vessels to react with aneurysm formation in the presence of ischaemia: the capillaries react first with microaneurysm formation. As the ischaemia aggravates, initially the veins and then the arteries are involved and show aneurysm-like pouchings.

From the observed findings in this paper some comments can be made as to the nature of arteriovenous anastomosis formation which is the most well-known feature of Takayasu's disease. In case 6 (Fig. 15) we can observe a typical instance of arteriovenous anastomosis formation which fits well to the original description by Takayasu. Fig. 15 shows that the major arterial and venous braches have anastomosed at their crossings and that vessels distal to the crossings are completely obliterated. One observes further that effective flow takes place only in these anastomosed larger vessels, while retinal vessels of lesser order do not show fluorescein and therefore seem obliterated. In Fig. 6 one sees another instance of arteriovenous formation in the peripheral fundus in a case less advanced than case 5. Here the pre-esisting communicating channel has opened up to form direct communication between artery and vein. The minor vessels distal to the anastomosis have obliterated. Case 4 shows a third and less characteristic instance of pre-papillary vascular-loop formation. A number of vascular loops protrude anteriorly from the optic disc in a broom-like fashion. Through fluorescein these bunch of capillaries showed immediate filling of the dye followed by rapid leaking out of the vessels into the vitreous body. Though this type of neovascularisation does not deserve, strictly speaking, the designation of arteriovenous anastomosis, it is observed rather frequently in Takayasu's disease. It is sometimes a transient and may undergo spontaeous regression as has occurred in case 4.

Fluorescein studies in Takayasu's disease have shown that the retinal vessels show increased permeability against fluorescein through the vascular wall whenever the circulation in the retina is impaired over a certain degree. The increased permeability results either in leakage or extravasation of fluorescein or in retention phenomenon of the dye within the vessel

wall. In two instances, namely in Case 1 and 4, the impaired permeability proved to be reversible after normalisation of fundus circulation through by-pass graft to supplement the occluded carotid. From the ophthalmological point of view this method of operation seems to be far superior to the hitherto prevalent removal of the carotid body conducted with the aim to suppress the annoying attacks of syncope in this disease. As far as the prognosis as to vision is concerned, adequate blood supply to the eye via the implanted by-pass vessel graft proved to be the most effective remedy to cure the diseased fundus condition.

The features of the Takayasu's disease as have been presented in the present paper seem to allow of a statement that the disease can be interpreted as a sequence of fundus reaction against decreased blood supply to the eye of an extremely gradual progress. In other words, the eye seems to be exempt from primary angiitis-like processes as usually occur in the aorta and its major tributary arteries in this disease. Tissue hypoxia has been known to be the cause of a variety of retinal diseases including retrolental fibroplasia. Takayasu's disease can probably be regarded as a typical instance of retinal vascular response in the presence of tissue hypoxia.

Apart from fluorescein findings, the presented cases show interesting characteristics as regards intraocular pressure and gonioscopic aspects. In four eyes out of 3 patients in advanced stage of the disease (Cases 4, 5& 6) complete goniosynechia has formed spontaneously reaching a uniform height at the line of Schwalbe associated with rubeosis of the iris and ectropium of uvea at the pupillary margin. In spite of apparent total obstruction of drainage channel the intraocular pressure stayed around 20 mmHg in all the four eyes observed. The intraocular pressure during the early stage of Takayasu's disease has been invariably found to be extremely low, usually less than 10 mmHg. This intraocular hypotention is to be understood as a consequence of decreased aqueous formation due to poor blood supply to the ciliary body. This will explain why the intraocular tension stayed within normal range in the four eyes with total goniosynechia formation. The absolute glaucoma which set in 5 days after vascular surgery in Case 4 is also to be understood as due to increase of aqueous flow to a normal level following improved circulation in the ciliary body. The presence of total goniosynechia, rubeosis iridis and uveal ectropium has been held as characteristic feature of haemorrhagc glaucoma and has been known to occur in thrombosis of the central retinal vein and in some cases with severe diabetic retinopathy. It is already an accepted finding that microaneurysms and increased permeability of vascular wall against fluorescein are prone to occur in these two retinal conditions. As regards fluorescein fundus findings and behaviour of the iris Takayasu's disease in late stages can be said to possess considerable common features with diabetic retinopathy and postthrombotic retinal conditions.

Summary

Six cases with Takayasu's disease in various stages were studied with fluorescein fundus angiography. All cases were female subjects and demonstrated angiographically confirmed obstruction of the common carotid artery.

The initial response of the fundus to the decreased arterial blood supply consisted in dilatation and aneurysm formation of retinal vessels. These two types of reaction occurred first in capillaries and later in veins and arteries as the disease progressed. In two cases normalisation of the fundus condition took place immediately after establishment of sufficient retinal circulation by means of by-pass graft between the aorta and the internal carotid. The cases show that capillary microansurysms and vascular engorgements in Takayasu's disease are reversible processes at least during its early stage.

Three types were distinguished in the arteriovenous anastomosis formation in the retina. In the less advanced stage of the disease direct communication between artery and vein was formed through apparent widening of preexisting vascular bridge in the periphery. As the disease advanced, direct anastomosis was formed between arteries and veins at their crossings. Both types of anastomosis formation resulted in obliteration of retinal circulation distal to the anastomosed vessels. As a third type of anastomosis-like vascular response a bunch of capillary loops were formed in front of the optic disc reaching anteriorly into the vitreous.

The studies indicate that impaired blood supply to the retina or extreme decreased in retinal arterial pressure is the cause of pathological findings in Takayasu's disease. Evidence has been lacking which suggests the existence of primary angiitis-like processes in the fundus in this disease.

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STUDIES ON THE VISUAL EVOKED RESPONSE (VER)

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REPORT I. THE LATENCY OF VER IN RABBITS

A number of studies on the latency of the VER in rabbits have been reported (Kormüller[3], Thompson, Woolsey & Talbot[8], Nakagawa, Doty, Monnier). As the VER is usually superimposed on the EEG or other potential changes on the head, its recorded wave form is variable from time to time and case to case. Many observations have been made by means of Dawson's superimposition technique. As far as the measurement of the latency is concerned, the rising point of the primary wave is not clear. Therefore Wang, Bartley and Van Hof[9] measured the peak latency. Recently these difficulties have been overcome owing to the computer technique. The present study of the VER in rabbits which are in their physiological condition has been carried out taking into consideration the following proboems. (1) Investigation of the rising foot of the initial wave of the VER. (2) Differences of the latencies of the VERs depending upon the recording points on the dural surface. (3) Comparison between the latency of the VER and that of the electrically elicited cortical response. (4) Influence of flash intensity on the latency of the VER. (5) Latency of on- and off- responses.

Methods

The unanesthetized adult albino rabbits weighing more than 2.0 kg were put into the fixing apparatus with only their heads exposed to observe under physiological conditions. Before the scalp was incised a 1% procaine anesthesia was administered. Without injuring the dura, a small hole was drilled into the skull. In mapping out the latency of the VER, the position of the leading points were decided at 3, 6, 9 and 12 mm lateral to the lambda, and anteriorly at 3, 6, 9, 12, 15 and 18 mm respectively. The leading points were decided at 9 mm anterior to the lambda and 6 mm lateral to the midline in order to determine the latency of the VER and that of the cortical response by electrical stimulation, to measure the latency of on- and off-responsəs and to ascertain the relationship between the flash intensity and the latency of the VER.

The VER was recorded by using a silver wire electrode 5 mm in length with the tip being 0.2–0.3 mm in diameter. An indifferent electrode made of silver plate (5×10 mm) was placed on the surface of the frontal bone. A 10 μ sec. flash of white light from a strobotron tube was used as the stimulus. The maximum intensity of this light was 1.4 Joules per flash and the amount of illumination was reduced by neutral filters calculated from a density of

0.17 to 2.56. A 1000 lux tangsten bulb was used for the observation of the on- and off-responses. A time constant of 0.01 sec. was usually used for the observation of the VER. When electrical stimulation was used the upper lid was widely resected and the retrobulbar portion of the optic nerve with its dural sheath was partially exposed. A concentric electrode for stimulation was inserted into the exposed optic nerve in close proximity to the eye ball.

Signals from the active electrodes were amplified by a condensorcoupled amplifier (AVB-1) and displayed on a two-beam oscilloscope (VC-6) and a medical data proceeding computer (ATAC-401). An average of 40–80 responses was usually recorded. Recordings were made of the VER, ERG and the optic nerve resonse using two at a time interchangeably. Two beams were used in the programing of the computer. Each beam consists of 200 addresses and their intervals were equally divided. If the analysis time is 125 msec., the time interval of each address is 0.63 msec., if the analysis takes 62.5 msec., the time interval becomes 0.31 msec. After the programing it is possible to observe the amplified VER by the expansion of the beam. Therefore the smallest error can be detected in the measurement of the latency of the VER. The experiment was carried out under relatively photic adaptation (50 lux in front of the eye). The beams of the oscilloscope and computer were started with the onset of a light flash. In this paper upward deflections in the records indicate positivity at the recording electrode.

Results

1. Investigation of the rising foot of the initial wave of the VER.

Figure 1 shows the distinctive character of the response related to the excitability cycle in the rabbit's visual cortex. Paired electrical stimuli were applied to the contralateral optic nerve at the interval of 30 msec., then the typical cortical response was elicited by the first shock and only small waves by the second shock. The latter may be an entire aspect of the presynaptic response which can be recorded even during the refractory period in the cortex. There can be no doubt that a positive hump preceding the large cortical response is the initial part of the electrical sign of the incoming presynaptic volley. Accordingly, the measurement of the latency of the cortical response was made from the onset of stimulation to the point between the first small hump and the following risig phase as indicated by an arrow in Fig. 2A. Figure 2B shows the rising foot of the response in the visual cortex produced by electrical stimulation to the optic nerve. In this figure, however, the upper portion of the primary cortical response is omitted. The continuous line is made up of the addresses which appear in the computer. Supposing the response in the visual cortex is divided in two, the dotted lines then represent the presynaptic volley and the primary response of the VER. In other words the response shown by the continuous line is the algebraic sum of both responses. There may be some possibility that the net cortical response starts a little ahead of the point which is referred to here.

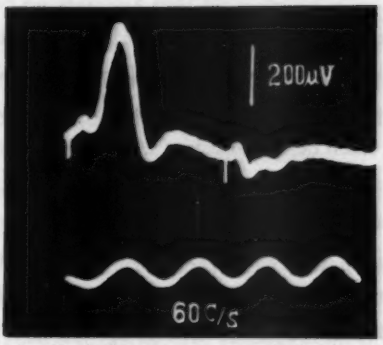

Fig. 1. Cortical response to paired electrical stimuli to the contralateral optic nerve. The time interval between the first shock and the second shock is 30 msec. The typical cortical response was elicited by the first shock, whereas only the presynaptic response was elicited by the second shock.
Electrical stimuli: 6V. Time constant: 0.01 sec.

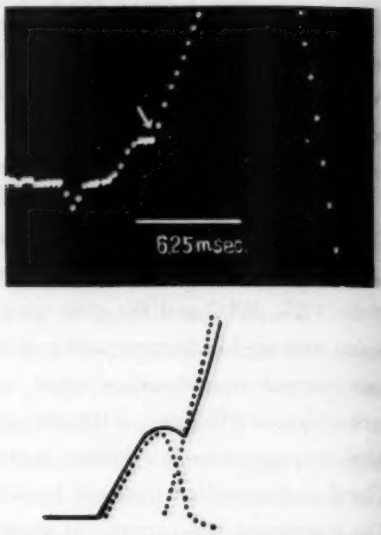

Fig. 2. The rising foot of the cortical response produced by electrical stimulation to the optic nerve.
A. The latency of the cortical response was measured from the cessation of a shock to the point indicated by an arrow. The record is the average of 92 responses.
B. The dotted lines represent the presynaptic response and the primary wave of the cortical response. The continuous line indicates the cortical response which is the algebraic sum of both potentials.

In fact, however, such a starting point cannot be determined with any amount of precision. Even if there would be an error, it would be slight or negligible.

The cortical evoked response is not so synchronous in nature as the electrically elicited one. Therefore the presynaptic response to photic stimultion could not be demonstrated as distinctly as in the latter. Figure 3 shows two examples of a rabbit's VER; the presynaptic response is relatively clear on the upper beam, but is obscure on the lower beam. In both cases the latencies of the VERs were measured from the onset of the flash to the points indicated by arrows in the figure.

2. Differences of the latencies of the VERs depending upon the recording points on the dural surface.

Figures 4 and 5 show the wave forms and latencies of the VERs taken from various points on the dural surface. The longest latency of the VER was 19.5 msec. at a point 3 mm lateral to the lambda and 18 mm anterior; the shortest latency was 15.1 msec. at a point 6 mm lateral

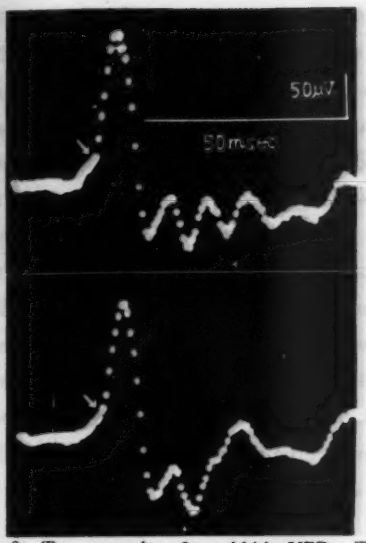

Fig. 3. Two examples of a rabbit's VER. The presynaptic response is relatively clear on the upper beam, but is obscure on the lower beam.
A. Flash: 1 cps. Dark room.
B. Flash: 0.2 cps. Light room (50 lux). The records are the average of 53 responses.

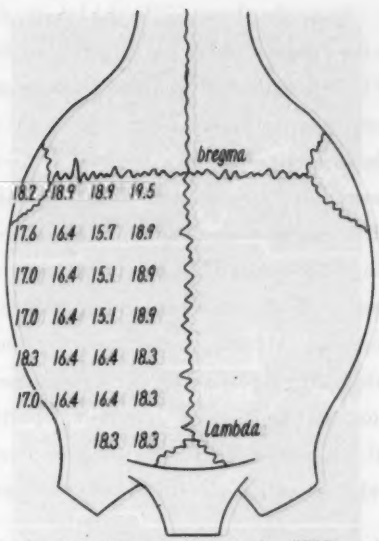

Fig. 4. Latencies (msec.) of the VERs taken from various points on the dural surface. Recording points were fixed at 3mm by 3 mm.

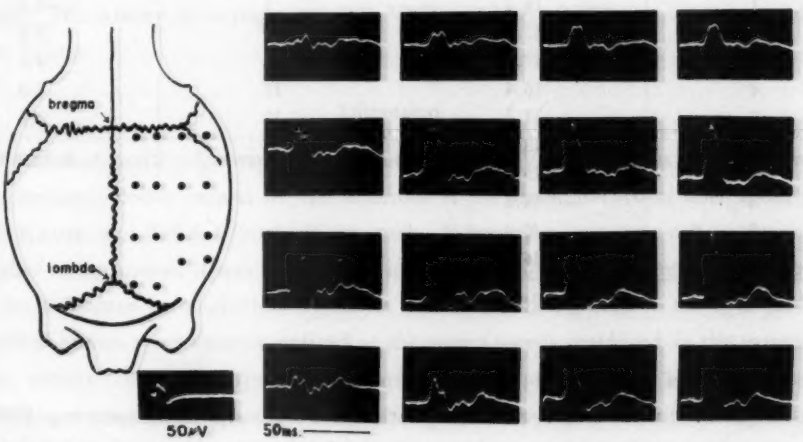

Fig. 5. Wave forms of the VERs taken from various points on the dural surface. The recording points were fixed at 6 mm by 3 mm.

to the lambda and 9–12 mm anterior to the lambda. The difference between the longest latency and the shortest was 4.4 msec.

3. Latency of the VER and the electrically elicited cortical response.

From the above results the latency of the VER in many cases was measured at 6 mm lateral to the lambda and 9 mm anterior to the lambda. Table 1 shows the latencies of the VERs of 10 unanesthetized rabbits. The average was 16.6±1.05 msec. which does not differ much from those reported so far. It should be noticed that the standard deviation is very small. These results were drawn when the eye was illuminated by a 1.4 Joule xenon photo flash which was reduced by a neutral filter of 0.17 density at 15 cm in front of the eye. The latency of the VER was prolonged as a matter of course when the intensity of the stimulus was reduced. When the intensity of the stimulus was reduced by a neutral filter, 0.17 to 2.56 in density, the latency of the VER was prolonged in proportion to the increases of the density (Fig. 6). The time interval between the latency of the optic nerve response and that of the VER was investigated using 5 rabbits (Rable 2), and the average was 4.3±0.46 msec. When electrical stimulation was given to the retrobulbar portion of the optic nerve, the average latency of the cortical response was 3.1±0.9 msec. in 5 cases. The difference between the latency of the VER and that of the electrically elicited cortical response was 13.5 msec.

Table 1. Latency of VER 10 unanesthetized rabbits (msec.)

Case No.	Latency of VER
1	16.4
2	17.0
3	17.0
4	16.4
5	17.0
6	18.9
7	15.8
8	14.5
9	16.4
10	16.4
Average	16.6±1.05

Table 2. Time interval (msec.) between latency of the optic nerve response and that of VER

Case No.	Time interval
1	4.4
9	3.8
11	4.4
12	5.8
13	3.8
Average	4.3±0.46

4. Latency of on- and off- responses.

A tangsten bulb was employed as the photic stimulation and its intensity was 1000 lux in front of the eye. As Pearlman[7] reported "lighton" gave an effect similar to the conditions flash and "light-off" gave an effect similar to the test flash in the VER when a long light flash was used. Therefore the off-response was facilitated or inhibited depending upon the duration the light stimulus. In Fig. 7 when the duration of the flash was 75 msec., the off-response to the photic stimulation was absent, but when it was increased to 210 msec., it was clearly

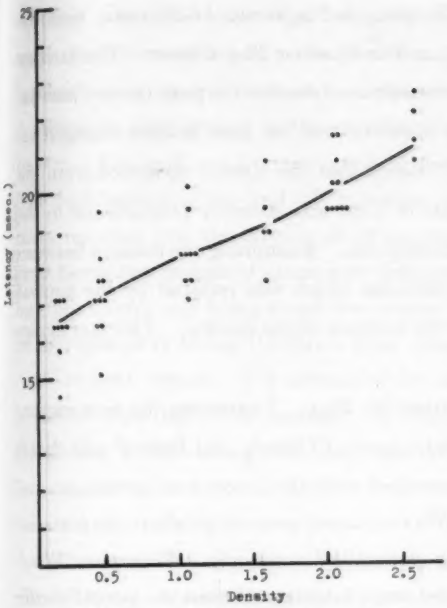

Fig. 6. Influence of flash intensity on latency of VER.

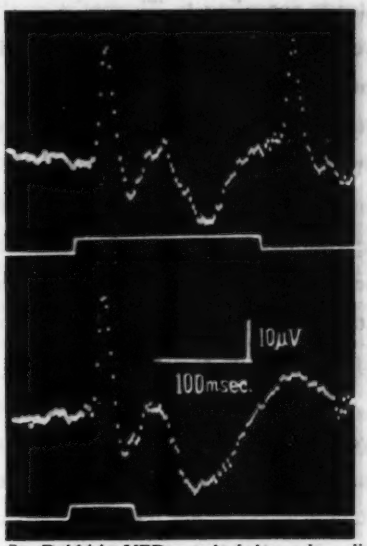

Fig. 7. Rabbit's VERs evoked by a long light flash.
A. The duration of a light flash: 210 msec.
B. The duratin of a light flash: 75 msec. The records are the average of 43 responses.

evidenced. The latency of on-response of the VER was 18.3 ± 0.72 msec., and that of shorter than the former.

Discussion

The first small positive hump prior to the initial wave of VER in rabbits may be equivalent to the presynaptic volley caused by the activities of the thalamo-cortical fiber about which Chang & Kaada[1] and Perl & Whitelock[6] reported. When the presynaptic volley was recorded using higher sweep speeds, it was further split into two or three small humps. It is probably due to the difference in conduction velocities of several fiber groups in the optic pathway. Such divided humps were scarcely noticed at the sweep speeds employed in the experiment. In many rabbits the primary response appears as a large positive wave which has masking effects on the presynaptic volleys with the exception of the first one. It may then by reasonable to consider that the cortical response initiates at the point between the first positive hump and rising phase of th large primary wave. In fact when the visual cortex was depressed two small humps were recorded as the presynaptic response (Fig. 1).

As to the latency of the VER, Kornmüller[2] and Fischer[2] reported that it was about 30 msec., and that it could not go below 20 msec. even if a very intense stimulation were given. The

latency according to Thompson et al[8]. was 19–29 msec., to Nagakawa 17–30 msec. with the average being 21 msec., to Sawamoto 13–19 msec., and to Monnier 23± 6 msec. The latency obtained here was 16.6±1.05 msec. Concerning the relation between the peak latency and the intensity of photic stimulation, Wang and Bartley observed that the peak latency changed inversely with the intensity of the light. Van Hof[9] stated that the latency measured from the start of the flash to the apex of the cortical response in a cat was inversely proportional to the logarithm of flash intensity in the intensity range investigated. Examining the relation between the latency of the VER and the intensity of the stimulus which was reduced by the neutral filters, the latency was prolonged in proportion to the increase of the density. This fact agrees with the results of Van Hof.

The visual cortex was delimited as the area striata by Rose. Examining the area responsive to electrical stimulation of the contralateral optic nerve, O'Learly and Bishop[5] said that it was more extensive than Rose's area striata. It extended medially across area peristriata, and laterally across Rose's zone of transition between area striata and area occipitalis to the posterior pole of the hemisphere and probably entered area parietalis 3 anteriorly. Thompson, Woolsay & Talbot[8] stated that the visual cortex extended more lateralward than the lateral border reported by O'Learly & Bishop, and that area occipitalis was included in it. Drilling as small a hole as possible in the skull to insert an electrode for the purpose of observation under physiological conditions, the VERs in Fig. 4 were recorded through the dura. It is difficult to decide the accurate extent of the visual cortex, but it may be possible to ascertain its outline by means of the amplitude and the latency of the VER. Bishop reported that there existed a one-to-one point relationship between the retina and the visual cortex, but the projection pathway from one point of the retina to a corresponding point of the cortex was multiple. On the other hand, Thompson obtained a point-to-point relationship between the retinal and cortical response areas by selecting the point in the visual field which gave the largest VER with the shortest latency. Examining the cortical responses to local electrical stimulation of the retina, Doty and Grim accepted the existence of retinocortical relationship which Talbot and Marshal had already discovered. In this experiment the VER was observed from the surface of the dura, so that it is difficult to compare the results of this experiment immediately with the results regarding the response derived from the pia and the cortical surface. Figure 5 seems to show the localization of the visual cortex which is responsive to photic stimulation to some extent. It coincides with the report by Thompson that the latency is short where the response is large. Lennox and Madsen[4] explained that the production of an off-response was dependent upon flash duration. According to Pearlman[7] the off-response did not occur with a flash duration of less than about 100 msec. Van Hof[9] said that the generation of the off-response

required a flash duration of at least 110 msec. in the anesthetized cat. Approximately the same results were obtained in the present study, though the off-response of the VER was clearly observed in several cases at a comparatively short flash duration of 30–40 msec. Such a difference may be due to the experimental conditions such as adaptation and stimulus intensity. This will not be mentioned in detail as it goes beyond the purpose of this paper. The peak latency of on- and off- responses was investigated by Wang and Van Hof. Both of them reported that the latency of off-response was far shorter than that of on-response. Bishop found two groups of fibers with different conduction velocities in the optic nerve of rabbits, but Granit and Marg found five groups. On the other hand, Yokoyama et al.[10] discovered four groups of fibers; the fastest fiber group had a specific characteristic responding to only "off" of light stimuli. The latency of the off-response of evoked potential in the optic nerve is shorter than that of on-response. It should be noted that a part of the difference between the latency of the on- and off- responses of the VER is already apparent in the optic nerve.

Summary

Measurement was made of the latency of the VER of unanesthetized adult albino rabbits. The VER was recorded from the dural surface and the average was obtained by means of an electric computer. The results obtained were as follows:

1) In the rabbit's VER there exists a small hump preceding the net cortical response. From the results obtained here it may be concluded that the first positive hump is an electrical sign of incoming presynaptic volleys. The measurement of the latency of the VER was made from the onset of photic stimulation to the point between the first small hump and the subsequent rising phase.

2) The wave form and latency of the VER obtained from the dural surface varied depending upon recording points. The largest response with the shortest latency was recorded from a point 9 to 12 mm anterior to the lambda and 6 mm lateral to the midline of the skull surface

3) When a xenon photo flash 1.4 Joules was reduced by neutral filters, 0.17 to 2.56 in density, the latency of the VER was prolonged in proportion to the increase of the density. The latency of the VER was 16.6 ± 1.05 msec. when the eye was illuminated by xenon photo flash which was reduced by a neutral filter, 0.17 in density. The time interval between the latency of the optic nerve response and that of the VER was 4.3 ± 0.46 msec. When electrical stimulation was given to the retrobulbar portion of the optic nerve, the latency of the cortical response was 3.1 ± 0.9 msec.

4) The observations were made also on the VER evoked by a long light flash. The intensity of the flash was 1000 lux at the corneal surface. In this case, the latency of on-response was 18.3 ± 0.72 msec., and that of off-response was 14.8 ± 0.75 msec. The off-response

was facilitated or inhibited according to the duration of the light stimulus, and its latency was shorter than that of on-response.

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REPORT II. THE RETINO-CORTICAL TIME

In the previous paper the latency of the VER in rabbits was mentioned. Another important problem relating to this is the retino-cortical time, about which Laue & Monnier[4], and Laue[3] reported. The time relation between the ERG and the activity of the optic nerve has not yet been sufficiently clarified. In the present study the time relation between the two was observed and the retino-cortical time was investigated.

Methods

The unanesthetized adult albino rabbits, weighing 2.5–3 kg were mounted on the stereotaxic apparatus. A 1% atropin solution was used to dilate the pupil. The room temperature was maintained at 35°C and higher. The prechiasmal portion of the optic nerve, 10 mm posterior to the papilla (aperture of the optic canal), was disclosed by removing a part of the frontal bone and frontal lobe. The leading electrode was inserted into the prechiasmal portion of the optic nerve from which the optic nerve response was recorded. Since it is possible to exclude completely the influence of the ERG, and in order to avoid operative injury to

the eye ball this portion was chosen. An electropolished steel electrode was used so as to record the ERG and the impulse discharge of the retinal ganglion cell simultaneously for the purpose of observing the time relation between the two. The tip of the electrode was about 5μ in diameter and the interelectrode resistance was less than 15 kΩ. The electrode was insulated except for 10μ in length at the tip and mounted on a micromanipulator, and was then thrust into the retina via the vitreous humour. At this point the most important thing is to minimize injury to the eye ball. In addition to this a decrease in the temperature of the eye influnces the time relation between responses produced in the retina and the optic nerve. Therefore only a part of the upper lid and the limbal portion of the bulbar conjunctiva was resected. Precaution was taken to control ocular tension and reduce bleeding to a minimum, by making a scleral incision as small as possible.

In recording the VER a subcutaneous injection of 1% procain was administered to the rabbit and its scalp was resected. In order to prevent injury to the dura a small hole was drilled into the skull at a point 9 mm anterior to the lambda and 6 mm lateral to the midline, where the latency of the VER was the shortest. The VER was recorded at this point of the dura. A silver wire 5 mm in length with a tip of 0.2–0.3 mm in diameter was used as a leading electrode.

The ERG was picked up with a contact lens of low Vacum. An indifferent electrode made of silver plate (5 × 10 mm) was placed on the surface of the frontal bone. A 10 μ sec. flash of white light from a strobotron tube was used as the stimulus. The maximum intensity of this light was 1.4 Joules per flash and the amount of illumination was reduced by a neutral filter calculated at a density of 0.17. A 1 cps. flicker was mainly used.

The recording system and averaging technique and illumination of the experimental room are almost the same as described in the previous paper.

In this paper upward deflections in the records indicate positivity at the recording electrode.

Results

1. Time relation between the optic nerve response and ERG.

There is general agreement that the positive components immediately following the negative P III of the ERG are representations of excitatory processes initiated in the retina. The peak of so-called a_1-wave, therefore, indicates the leading edge of such excitatory potential changes which may directly or indirectly be concerned with the driving of the activity of the next neurons i.e. the retinal ganglion cells. As is clearly shown in Fig. 1, the latency of the optic nerve response was longer than the peak latency of the a_1-wave, whereas it was a little shorter than that of the a_2-wave. The results obtained from 10 cases are presented in Table

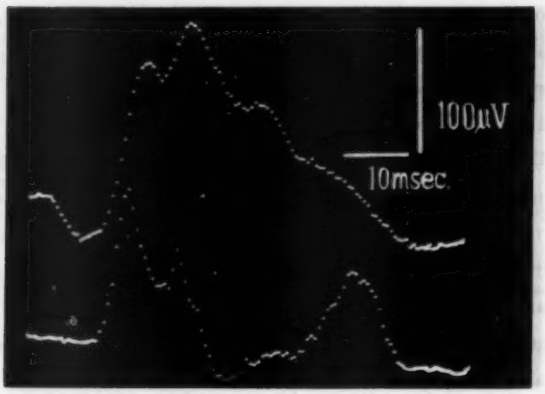

Fig. 1. Simultaneous recording of ERG (upper beam) and optic nerve response (lower beam). The record is the average of 30 responses. Time constant: 0.01 sec. Flash: 1 cps.

1. In this table "time interval" means the difference between the peak latency of the a_1-wave and the latency of the optic nerve response.

2. Time relation between the impulse discharge of retinal ganglion cells and the peak latency of the a_1-wave.

Figure 2 shows two cases (A and B) of the ERG which were recorded in the vitreous humour (upper traces) and in the inner layer of the retina at the posterior pole of the eye (lower traces). Spikes superimposed on the retinal ERG were identified as the unit activity of the ganglion cell according to the following reasons :(1) The spikes are obtained within a depth of 10–20μ from the retinal surface. (2) The b-wave of the ERG recorded simultaneously with the spikes is positive[2]. (3) The size of the electrode employed here does not permit the recording of unit activity of the bipolar cells or other smaller cells. The time course of each component wave of the ERG in the vitrous humour corresponds almost entirely to that of the ERG from the ganglion cell layer. As Brown et al[2]. have already shown the time courses of the ERG from the vitreous humour and the cornea were almost the same.

It is a wellknown fact that the retinal ganglion cells usually respond repeatedly to a photic stimulus. The impulses recorded here may be the repetitive action of a ganglion cell in response to a light flash. Surveying the first spike among each train of impulses, the one with the shortest latency did not precede the peak of the a_1-wave in the time course and was delayed 0.6 msec. (Fig. 2A), and the one with the longest latency was delayed 4.9 msec. (Fig. 2B). This delay of the first spike was found to be confined to a range of 0.6 msec. to 4.9 msec. in all cases. Table 2 shows the latency of the impuse discharge of the ganglion cell, the peak latency of a_1-wave and the time interval between the two.

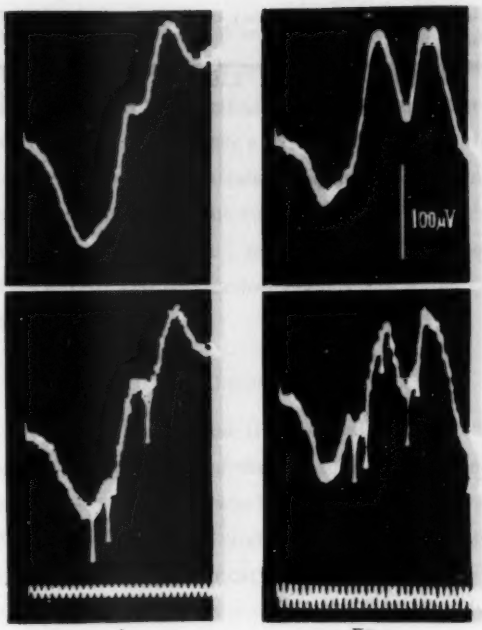

Fig. 2. ERGs and ganglion cell activities recorded from two animals (A and B).
Upper beams: ERGs in the vitreous humor.
Lower beams: ERGs and impulse discharges in the ganglion cell layer.
Time constant: 0.01 sec. Time marker, 1000 cps.

Table 1. Time relation between latency of evoked potential in the optic nerve and peak latency of a_1-wave (msec.)

Case No.	Peak latency of a_1-wave	Latency of the optic nerve response	Time interval
14	7.9	11.5	3.6
15	7.9	11.1	3.2
16	7.3	10.8	3.5
17	7.9	11.8	3.9
18	8.6	12.4	3.8
19	7.9	11.8	3.9
20	7.9	11.8	3.9
21	8.6	12.1	3.5
22	7.3	11.2	3.9
23	7.3	11.2	3.9
Average	7.9±0.45	11.6±0.47	3.7±0.23

Table 2 Time relation between peak latency of a_1-wave and latency of impulse discharge of the ganglion cell (msec.)

Case No.	Peak latency of a_1-wave	Latency of ganglion cell discharge	Time interval
1	7.6	11.1	3.5
2	7.6	12.5	4.9
3	7.6	9.7	2.1
4	8.6	12.6	4.0
5	7.6	8.5	0.9
6	7.6	9.9	2.3
7	8.1	13.0	4.9
8	7.6	8.6	1.0
9	7.6	8.2	0.6
10	7.6	10.1	2.5
11	7.6	11.6	4.0
12	6.9	11.8	4.9
13	7.4	12.3	4.9
14	8.6	12.6	4.0
15	8.6	10.9	2.3
16	8.6	10.1	1.5
17	8.8	12.8	4.0
18	8.6	11.6	3.0
19	8.6	12.1	3.5
20	8.6	11.1	2.5
Average	8.0±0.56	11.1±1.48	3.1±1.38

Table 3. Time relation between peak latency of a_1-wave and latency of VER (msec.)

Case No.	Peak latency of a_1-wave	Latency of VER	Retino-cortical time
1	7.6	16.4	8.8
2	7.6	17.0	9.4
3	7.6	17.0	9.4
4	7.6	16.4	8.8
5	7.6	17.0	9.4
6	8.8	18.9	10.1
7	8.2	15.8	7.6
8	7.6	14.5	6.9
9	8.8	16.4	7.6
10	7.6	16.4	8.8
Average	7.9±0.48	16.6±1.05	8.7±0.96

3. Time relation between ERG, evoked potential in the optic nerve and VER.

Table 3 shows the latency of the VER as reported in the previous paper, the peak latency of the a_1-wave, and the retino-cortical time which is the time interval between both latencies.

The retino-cortical time must be the sum of several synaptic delays and conduction time up to the cortex. It is clearly shown, together with the results mentioned in sections 1 and 2, that the initial one third of the retino-cortical time averaging about 3 msec. is needed for conveying visual information from the neurons in the bipolar cell layer to those of the optic nerve. A small difference between the latencies of ganglion cell firing (11.1 msec.) and optic nerve response (11.6 msec.) is ascribed to the conduction time from the retina to the prechiasmal portion. This time interval (0.5 msec.) may be reasonable from the view point of the conduction distance (12–13 mm) and conduction velocity (30 m/sec.) of the fastest fiber group responding to "on" of light[10].

Discussion

In 1954 Laue and Monnier[4] measured the interval between the retinal time and the cortical time to observe the conductibility of the visual pathway in man and rabbits. In this way the concept of the retino-cortical time was brought out. With regard to the evoked activities in the human visual system, the ERG and the VER are the only phenomena which can be recorded by means of electrophysiological methods. Therefore the retinocortical time is one of the best indicators for the diagnosis and follow up of any lesion in the visual pathway.

The observation showed that the mean value of the retino-cortical time is about 8 msec. in adult albino rabbits. This is largely in agreement with the results of Laue and Monnier[4]. However considerable differences are seen in values concerning the latencies of the ERG and the VER probably because a low intensity of light stimulus was used. This may be explainable in terms of the results of this study in that the retinocortical time could not be altered by a change in the stimulus intensity in contrast with an alteration in the latencies. The retino-cortical time in human adults, which was measured under approximately the same experimental conditions, was about 12 msec. as reported in a former study[9]. The retino-cortical time of human adults is approximately 4 msec. longer than that of rabbits, and such a discrepancy may be ascribed in part to the difference in the distance between the eye and the cortex.

The relationship between the a-wave or b-wave of the ERG and the optic nerve response was studied by Adrian and Matthews, Ponte and Monaco[7], Tomita, Mizuno and Ida, Bovie, Chaffee and Hampson, Granit, Bernhard, and Schubert[8]. According to Monnier[6], the retinal time was referred to as the period of time between the light stimulus and the onset of the b-wave only for the convenience of measurement. He did not agree with all of Bernhard's statement[1] that the b-wave is the first signal of the retinal impulses discharged into the optic nerve. The rising point of the b-wave would not always correspond to the peak of the a-wave depending on methods of recording and or experimental conditions. For example, when the a_1-, a_2- and a_3-wave appeared successively[5], it was difficult to find the initial rise of the b-

wave. Therefore in this study, the retinal time was measured from a light flash to the peak of the a_1-wave which is the reversal point where the positive deflection first appeared on the descending limb of the a-wave. As mentioned above, it should be stressed here that the peak of the a_1-wave is the leading edge of the corneal positive components of the ERG following the corneal negative P III.

When the measurement of the retino-cortical time is made according to the method used in this study, it may include not only the conduction time from the retina to the cortex, but the time interval between the onset of the activity in the bipolar cell layer and the initiation of the ganglion cell discharge. Of course delayed intervals in the lateral geniculate body and in the subcortex are additional problems which should be discussed. In the present study, however, analysis was confined to the events arising within the distal part of the visual pathway. Evoked response in the optic nerve can readily be recorded from the optic disc or retrobulbar portion, but it was taken from the prechiasmal portion in order to minimize operative injury to the eye and to prevent contamination of the ERG. When the impulse discharge of the ganglion cell was recorded, an electrode was thrust into the eye through a small incision made in the anterior sclera to avoid a decrease in the temperature of the retina. None of the first spikes in the ganglion cell discharges preceded the peak of the a_1-wave, and some delayed intervals were seen. This was true in the case of the optic nerve response. The mean value of such a delayed interval was 3.1 msec. in the case of the ganglion cell discharge and 3.7 msec. in the case of the optic nerve response. A slight difference of 0.6 msec. between the two can be explained by the conduction time of impulses from the retina to the prechiasmal portion of the optic nerve. It is conclusive now that, about one third of the so-called retino-cortical time is actually consumed within the retina and the remaining 4–5 msec. is concerned with the conduction time and synaptic delays in the subsequent proximal portion of the visual system. One of the evidences to support this has already been presented in the first report of this series of studies.

Summary

The retino-cortical time and the time relation between the ERG and the activity of the optic nerve was investigated in unanesthetized albino rabbits. The results obtained are as follows:

1) The retino-cortical time obtained by measuring the time between the peak latency of the a_1-wave and the latency of the VER was 8.7 ± 0.96 msec.

2) The impulse discharge of the retinal ganglion cell and the optic nerve response consistently occurred with some delayed intervals in relation to the peak latency of the a_1-wave.

3) The mean value in the latencies of the first spikes in the ganglion cell discharge was

11.1±1.48 msec. and it was 3.1±1.38 msec. longer than the peak latency of the a_1-wave.

4) The mean value in the latencies of the optic nerve response was 11.6±0.47 msec. and it was 3.7±0.23 msec. longer than the peak latency of the a_1-wave.

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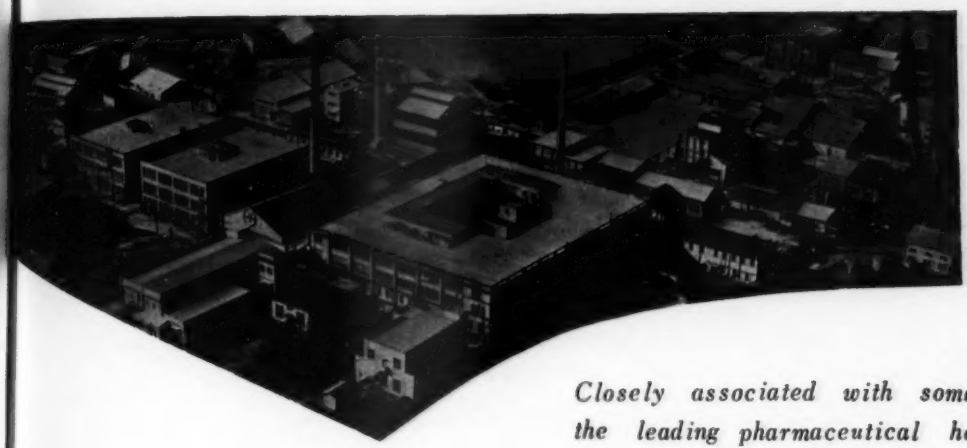

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